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Conjunctival Dacryocystorhinostomy
Steinsapir, Glatt, Putterman

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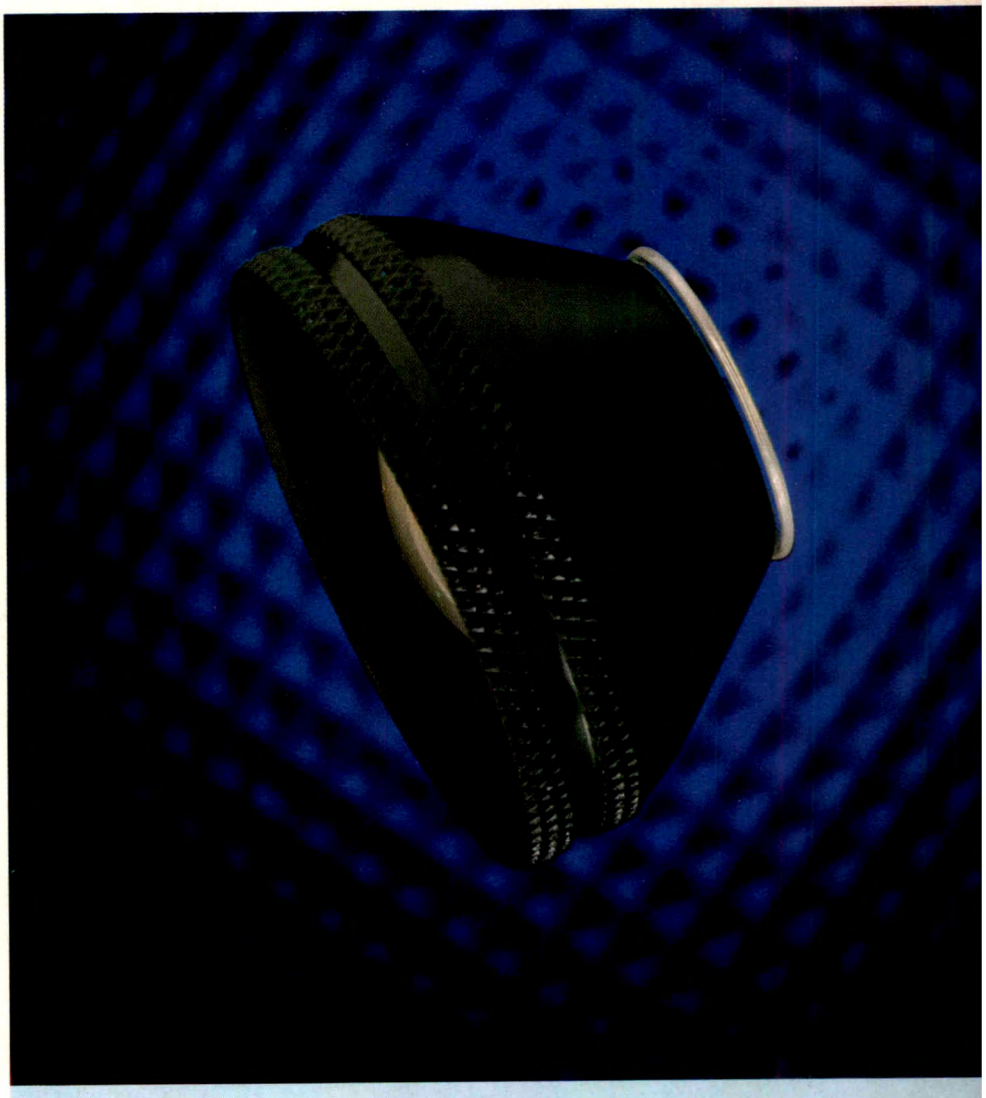

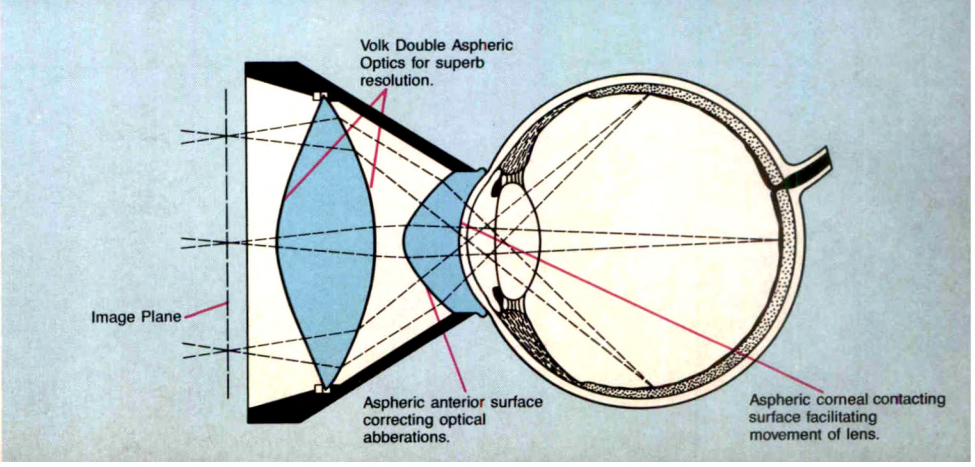

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A Computer Model for the Evaluation of the Effect of Corneal Topography on Optical Performance

Jon J. Camp, B.S.E.E., Leo J. Maguire, M.D., Bruce M. Cameron, M.S., and Richard A. Robb, Ph.D.

We developed a method that models the effect of irregular corneal surface topography on corneal optical performance. A computer program mimics the function of an optical bench. The method generates a variety of objects (single point, standard Snellen letters, low contrast Snellen letters, arbitrarily complex objects) in object space. The lens is the corneal surface evaluated by a corneal topography analysis system. The objects are refracted by the cornea by using raytracing analysis to produce an image, which is displayed on a video monitor. Optically degraded images are generated by raytracing analysis of selected irregular corneal surfaces, such as those from patients with keratoconus and those from patients having undergone epikeratophakia for aphakia.

CORNEAL TOPOGRAPHY studies show that good visual acuity as measured by Snellen tests is often found in patients who have surprising degrees of corneal irregularity.[1-10] These patients may describe image degradation, but such complaints are difficult to quantitate. Some investigators believe that Snellen visual acuity testing is an insensitive measurement of the types of visual degradation observed in patients with irregular topography. Contrast sensitivity testing is a more sensitive method of evaluating optical performance, but the clinical relevance of abnormal contrast sensitivity test results is not clear to most ophthalmologists. To address the need to correlate corneal topography with corneal optical performance, we developed computer software that acts as an electronic optical bench. An object and object vergence are defined by the software. The lens is the corneal surface as described by a topography analysis system. An image is generated by raytracing analysis of the object through the corneal surface.

Accepted for publication Jan. 24, 1990.

From the Departments of Physiology (Mr. Camp, Mr. Cameron, and Dr. Robb) and Ophthalmology (Dr. Maguire), Mayo Clinic and Foundation, Rochester, Minnesota. This study was supported in part by Research to Prevent Blindness, Inc., New York, New York, National Institutes of Health grant RR 02540, and the Mayo Foundation, Rochester, Minnesota. This study was presented at the 16th Cornea Research Conference, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, Sept. 23, 1989.

Reprint requests to Leo J. Maguire, M.D., Department of Ophthalmology, Mayo Foundation, 200 First St. S.W., Rochester, MN 55905.

Material and Methods

The objects are modeled to appear within an area 0.45 × 0.45 m located 6.0 m from the lens surface. The 6.0-m vergence was chosen because it approximates optical infinity. The 0.45 × 0.45-m field allows a 20/10 letter to be 5 × 5 pixels on the video monitor. The object can be a point source or a complex figure, such as a Snellen visual acuity chart, a chart of letters of variable contrast (Fig. 1), or any 512 × 512 pixel monochromatic scene.

The refractive surface used in the raytracing program is the cornea as represented by the Corneal Modeling System, a keratoscope-based topography analysis system.[11]

The Corneal Modeling System provides a power measurement and polar coordinates for each corneal surface point it measures (Fig. 2).

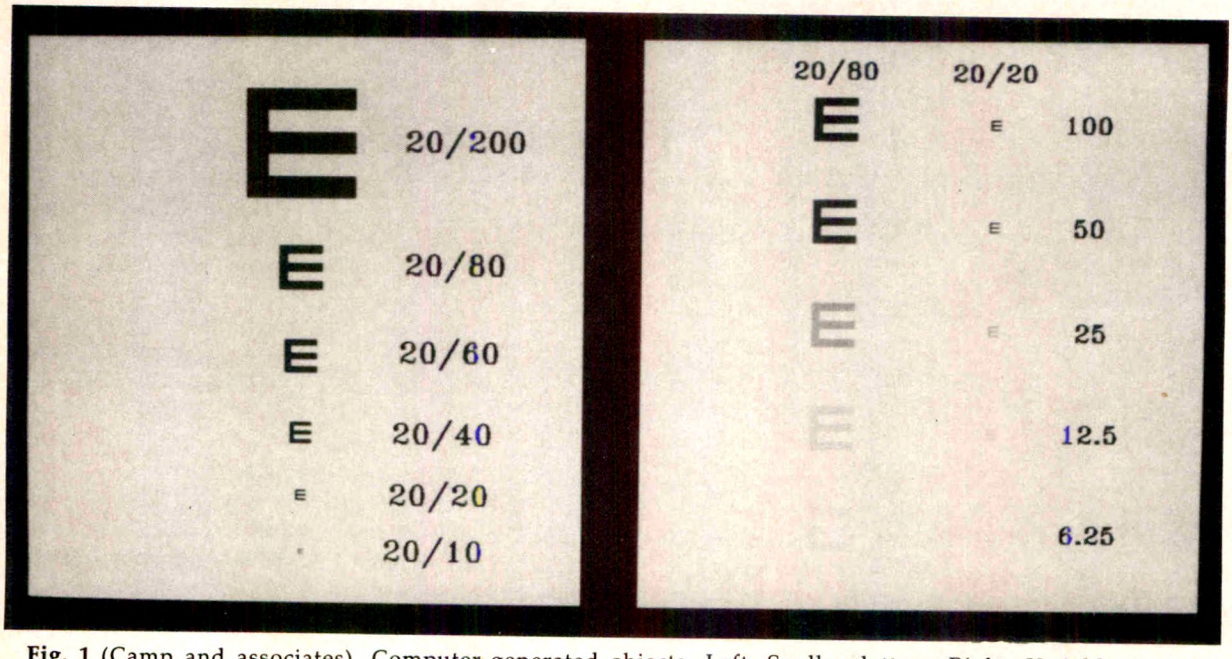

Fig. 1 (Camp and associates). Computer-generated objects. Left, Snellen letters. Right, Variable contrast letters. The images generated by raytracing analysis of these objects by three corneas with varying degrees of irregularity are shown in Figure 6.

These measurements are found in the processed data file of the Corneal Modeling System analysis. This information is used in the raytracing program, and we assume its accuracy. The Corneal Modeling System is known to provide accurate and reproducible readings when steel calibration spheres are measured,[12] but its accuracy and reproducibility in evaluating more complex surfaces is unknown.

An image is always a degraded version of the original object. Optical engineers commonly display optical degradation by a point-spread function.[13] This function shows the degree and location of blur caused by the refraction of a single point on the optical axis through the lens under investigation.

The electronic optical bench calculates a point-spread function by performing raytracing analysis through 2,560 corneal surface points (all measured points on the central ten keratoscope mires of the Corneal Modeling System). A simple raycasting technique based on lensmaker's equations is used as follows:

$$r_i = r_s - \left[\frac{n_o \cdot [r_s \cdot [(D_s \cdot s_o) - 1] + r_o]}{[(z_s \cdot n_o) \cdot [(D_s \cdot s_o) - 1]] - (n_i \cdot s_o)}\right] \cdot \left[z_s - \frac{n_i \cdot s_o}{n_o [(D_{ref} \cdot s_o) - 1]}\right]$$

where:

r_i = r coordinate of image point
r_s = r coordinate of surface point
z_s = z coordinate of surface point
D_s = diopter power at surface point
n_o = index of refraction outside eye (1.00)
r_o = r coordinate of object point (o for point-spread function calculation)
s_o = object distance
D_{ref} = reference diopter power (mean of 2,560 corneal surface points)
n_i = index of refraction of the cornea (1.3375)

The program calculates an in-focus image plane and magnification for each of the 2,560 corneal surface points through which the object point is refracted. The surface point and its corresponding in-focus image point are used to construct a ray, which intersects with a reference plane (that is, the plane in the image space of interest to the computer operator) (Fig. 3). Unless the operator directs otherwise, the program automatically displays the reference plane of best focus. In our method, the vergence of this plane is determined by calculating the mean power of the 2,560 corneal points through which the object point is refracted.

The method is best understood by viewing the point-spread function produced when a single object point is refracted through the

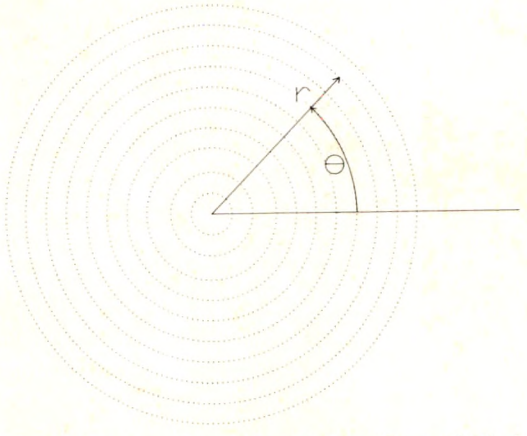

Fig. 2 (Camp and associates). The Corneal Modeling System represents the processed keratoscopic data in polar coordinates. Three variables locate each corneal point in space. Theta (TH) shows its hemimeridian location. Its distance from the calculated center point is r_s. Its sagittal location, Z, not shown, is determined by a proprietary algorithm. The raytracing program uses these data and the corneal power calculation of each point to make the point-spread function.

topography analysis representation of corneal surface power. The topographic maps of a normal cornea (Fig. 4) and a cornea with early keratoconus (Fig. 4) are used to demonstrate the raytracing method. The three eyes have excellent visual acuity and minimal refractive error. A cursor marks the position of keratoscope ring 10 in each display in Figure 4.

The point-spread functions derived by raytracing analysis of each of the corneal surfaces are shown in Figure 5. The data may be displayed on a linear or logarithmic scale. These figures show a linear scale. They are oriented in the same fashion as visual field displays.

Point-spread functions may interest optical engineers, but most clinicians prefer to view image degradation of familiar objects such as Snellen letters. Our method generates these images by convolving the Snellen object with the point-spread function of the cornea under investigation. This technique is commonly used in the field of optical computing.[13] Figure 6 shows the images obtained by refracting the 20/80 and 20/20 variable contrast Snellen targets shown in Figure 1 through the corneal surfaces shown in Figure 4. An image obtained by raytracing analysis of a patient from an earlier study[9] on epikeratophakia for aphakia is included as well.

The raytracing computations were performed on a MASSCOMP 5700 vector accelerator at the Mayo Biotechnology Computer Resource. The computational speed of this hardware allows calculation of a point-spread function for 2,560 corneal surface points in 0.167 second. An arbitrary 512 × 512 pixel object can be processed in under three seconds. Computer workstations such as the Sun 3 require an order of magnitude greater processing time. Images are reviewed, displayed, and evaluated with the aid of ANALYZE, a comprehensive interactive image analysis system developed by the Mayo Biotechnology Computer Resource.[14,15] The availability of this preexisting code precluded the need to develop original software for image display.

Results

A graphical representation of the point-spread function for three corneas shown is shown in Figure 5. A perfect lens system would focus all light on a single point in the image plane of best focus. The point-spread function of the normal cornea closely approximates such an output, but a small amount of signal spread is seen. The point-spread function of the cornea from the patient who underwent epikeratophakia shows a central peak but more central spread of signal than observed in the normal cornea. The point-spread function from the cornea with keratoconus shows a high-ampli-

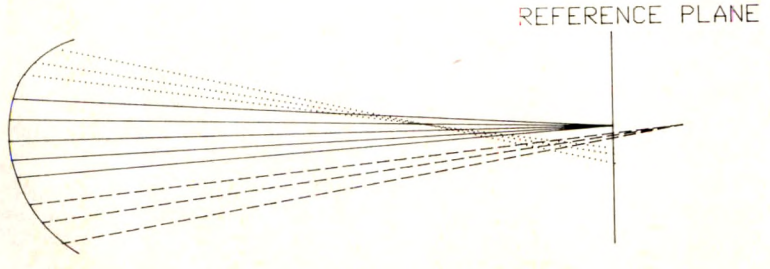

Fig. 3 (Camp and associates). Schematic representation of refraction through two hemimeridians of an irregular cornea. The reference plane is the plane shown by the raytracing analysis. Our method determines the point-spread function at the image plane of interest to the operator.

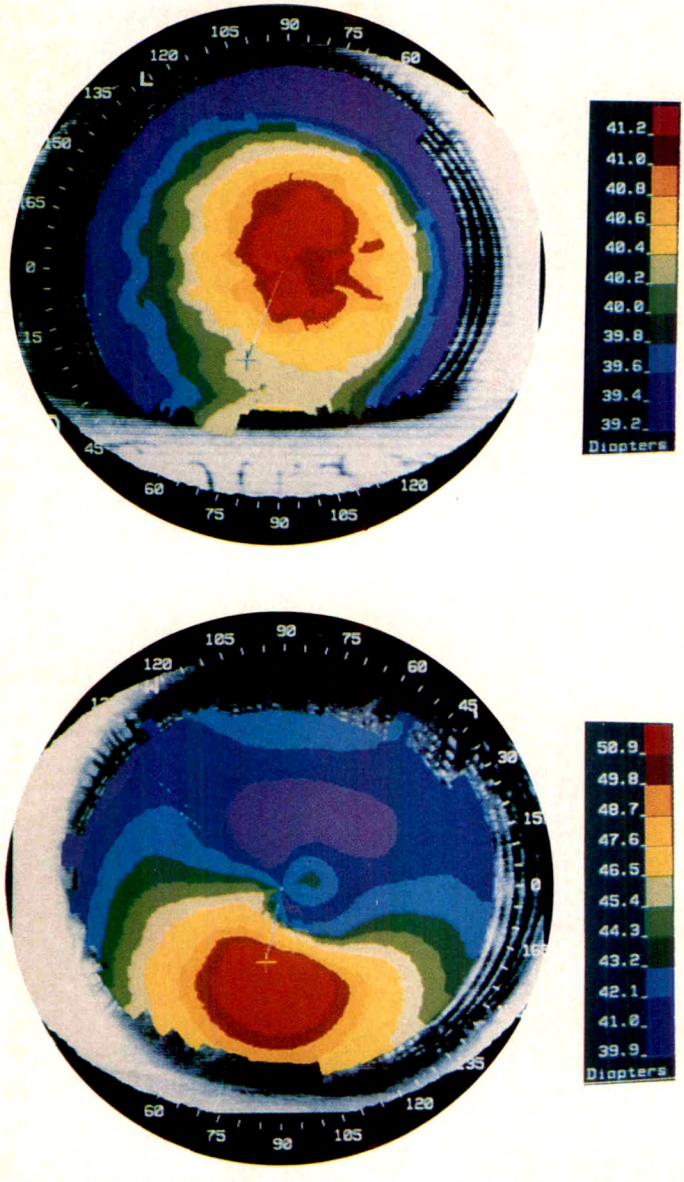

Fig. 4 (Camp and associates). Color contour maps of two corneal surfaces with different amounts of corneal irregularity. Top, Map of a normal patient with no keratometric astigmatism and uncorrected visual acuity of 20/10. Bottom, Map of a patient with keratoconus. Best-corrected visual acuity is 20/20 with a −2.50 sphere.

tude central peak and a low-amplitude asymmetric spread of signal.

Figure 6 shows the images from refraction of the variable contrast 20/20 and 20/80 letters through the two corneas shown in Figure 4 and the cornea of a patient who underwent epikeratophakia.[9] The image from the normal cornea shows excellent resolution of the 20/80 and 20/20 letters at all contrast levels. The output for the eye that underwent epikeratophakia for aphakia shows more image degradation, but the 20/80 letter is well visualized to 6.25% contrast. The 100% and 50% contrast 20/20 letters are degraded but recognizable. The lower contrast 20/20 letters are not discernable. The images from the patient with keratoconus have sharper borders than the images from the patient who underwent epikeratophakia, but they show a relative reduction in contrast. The higher contrast 20/80 letter shows an obvious ghost image that is not as apparent at lower contrast levels.

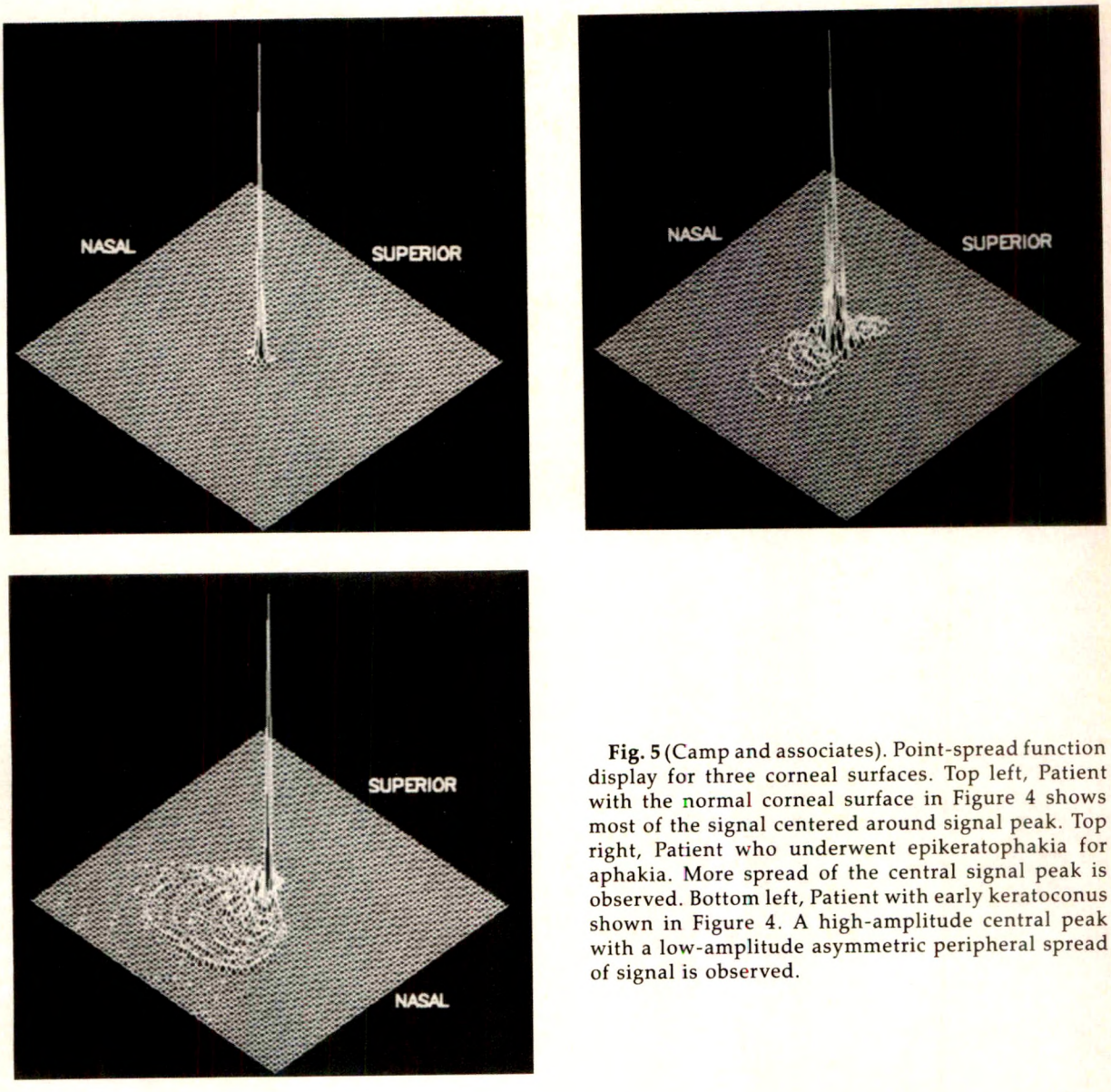

Fig. 5 (Camp and associates). Point-spread function display for three corneal surfaces. Top left, Patient with the normal corneal surface in Figure 4 shows most of the signal centered around signal peak. Top right, Patient who underwent epikeratophakia for aphakia. More spread of the central signal peak is observed. Bottom left, Patient with early keratoconus shown in Figure 4. A high-amplitude central peak with a low-amplitude asymmetric peripheral spread of signal is observed.

Discussion

Our electronic optical bench method is an initial attempt to bridge a gap that exists between technologies that describe irregular corneal surfaces (such as corneal topography analysis) and measurement methods that describe what the patient sees after the image encountered at the neurosensory retina is processed through to the occipital cortex (such as standard visual acuity testing and contrast sensitivity testing). We believe such a system is needed because methods currently used to evaluate keratorefractive procedures measure corneal optical performance indirectly or not at all. This status quo is not acceptable given the growth in the field of refractive corneal surgery.

Standard visual acuity measurements are adequate for evaluating corneal optical performance in comparative studies only when the physical optical system is assumed to be similar between groups. When the optical system degrades in an unknown fashion, as after keratorefractive corneal surgery, visual acuity charts with 100% contrast target letters are not as sensitive a measure of optical performance as they are when used for refraction of the normal

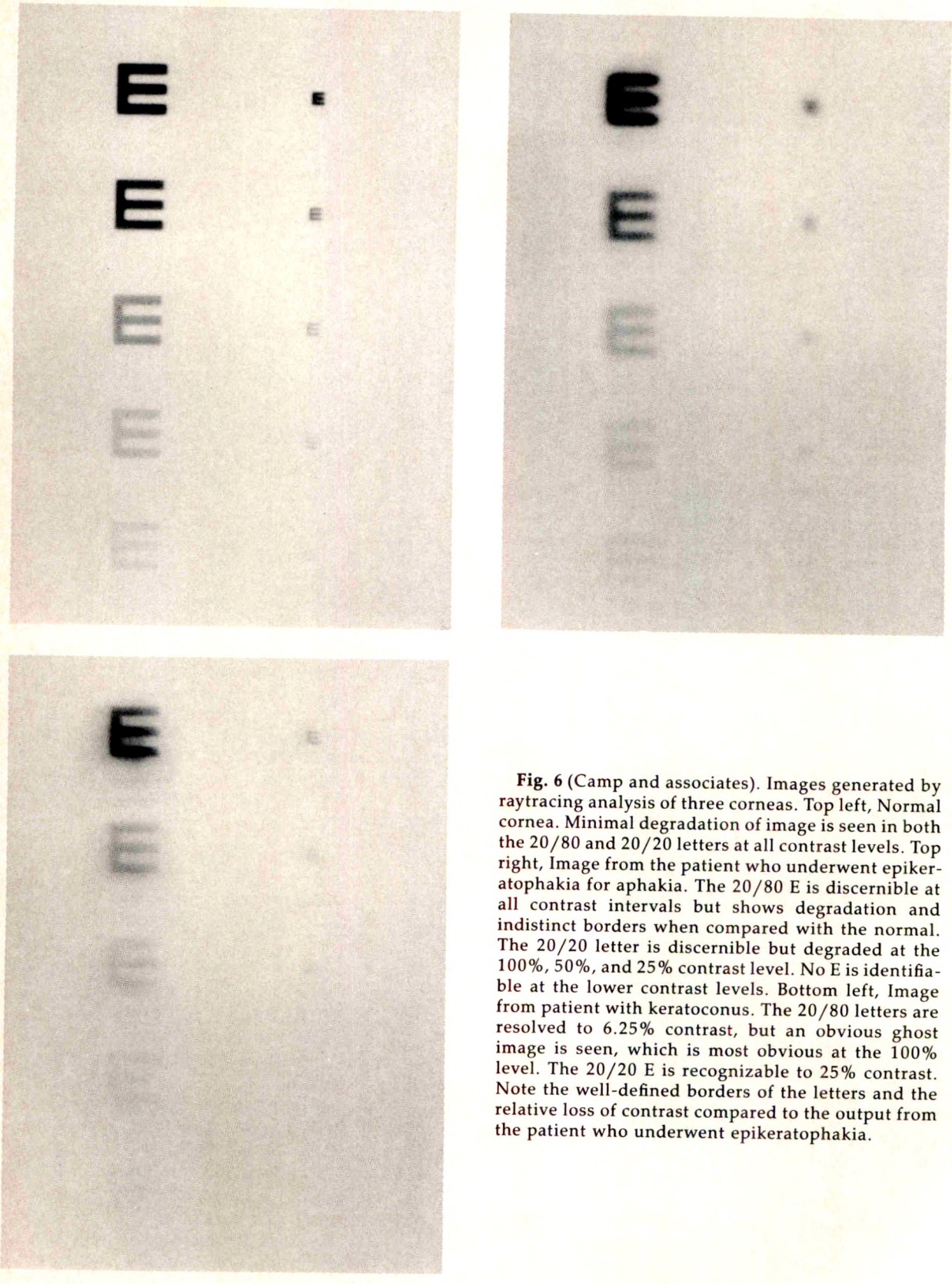

Fig. 6 (Camp and associates). Images generated by raytracing analysis of three corneas. Top left, Normal cornea. Minimal degradation of image is seen in both the 20/80 and 20/20 letters at all contrast levels. Top right, Image from the patient who underwent epikeratophakia for aphakia. The 20/80 E is discernible at all contrast intervals but shows degradation and indistinct borders when compared with the normal. The 20/20 letter is discernible but degraded at the 100%, 50%, and 25% contrast level. No E is identifiable at the lower contrast levels. Bottom left, Image from patient with keratoconus. The 20/80 letters are resolved to 6.25% contrast, but an obvious ghost image is seen, which is most obvious at the 100% level. The 20/20 E is recognizable to 25% contrast. Note the well-defined borders of the letters and the relative loss of contrast compared to the output from the patient who underwent epikeratophakia.

eye.[16] Such charts detect only gross abnormalities of visual performance.

The insensitivity of high-contrast visual acuity charts is well documented in many contrast sensitivity studies.[17-23] Topography analysis studies document that relatively severe degrees of corneal irregularity are compatible with visual acuities of 20/20 to 20/40.[3,7-10]

Vision scientists know that contrast sensitivity testing is a more sensitive method of testing optical performance than standard visual acuity testing when studying patients who have irregular optical surfaces. Unfortunately, problems limit the implementation of contrast sensitivity testing in clinical practice. Contrast sensitivity cannot gauge the optical performance of the cornea in isolation, because results are affected by confounding variables in the visual system, such as spectacle blur,[24,25] lenticular opacity,[26] retinal disease,[27-29] and optic nerve abnormalities, such as glaucoma and optic neuritis.[29] Controversy exists about the most appropriate method of testing. The reproducibility of some of these tests has been questioned.[30] Finally, and most importantly, the clinical ophthalmologist has difficulty interpreting the clinical significance of contrast sensitivity results and extrapolating abnormal findings to a patient's visual performance outside the laboratory.

Problems exist with the use of corneal topography analysis to evaluate surgical success after refractive surgery. The recently introduced topography analysis systems[1,11,31] have improved our understanding of the patterns of power distribution found in patients after refractive corneal surgery.[2,4-6,8-10] Unfortunately, the results of these topographic studies are descriptive and not easily adapted to statistical analysis. Inspection of the power maps provides no information on the optical performance of the cornea.

Our electronic optical bench method allows an approximation of corneal optical performance to be made by using the information provided by corneal topography analysis as a component of a larger software program. We emphasize that the method does not allow us to see through the eyes of the patient, which would require that we know how the visual system processes the degraded image. Rather, our method isolates and measures the optical performance of the corneal surface as directly as present technology permits.

By modeling refraction of familiar objects used in clinical practice, we believe this method shows the clinician that fairly severe degrees of image degradation from irregular surface topography can exist and still allow a small 100% contrast visual acuity test object to be visualized. The Snellen figures of the three corneas show that not all 20/20 visual acuity is the same. We believe this concept must be well understood by the public, eye care policy analysts, and eye care providers given the current and impending flood of refractive corneal surgical techniques and the recently popularized concept of pseudophakic correction of presbyopia.

Possibilities for the future include user-friendly interactive software that can alter object vergence and add spectacle correction and intraocular lens design to the raytracing analysis. Other improvements include analysis of a larger portion of the corneal surface area, analysis of surface points relative to the pupil position and pupil size,[32] and programs to evaluate glare. As these developments occur and improvements are made in topography analysis technology, electronic optical bench software should allow an increasingly accurate understanding of the contribution of corneal surface topography to visual performance.

If future testing finds that the output of the electronic optical bench correlates with conventional measures of visual performance, systems similar to the one described herein may provide a method of performing statistical analysis on the optical quality of the corneal surface after refractive surgical procedures. Our understanding of unusual visual phenomena often noted by patients after refractive corneal procedures may improve.[5,6,8,10,33] In an age when radial keratotomy, epikeratophakia, intralamellar implants, keratomileusis, excimer laser corneal ablation, and multifocal intraocular lens implants are under investigation, we believe that raytracing systems are needed to allow differentiation between irregular corneas with good optical performance and those with bad optical performance.

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A 16-Year Study of Conjunctival Dacryocystorhinostomy

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We reviewed a consecutive series of 79 conjunctival dacryocystorhinostomies performed over a 16-year period in 75 patients. Thirty-eight of 75 patients with canalicular blockage between the common canaliculus and the first 5 mm of the canaliculus as well as patients with common canalicular blockage who had failed previous dacryocystorhinostomy were treated with combined canalicular reconstruction, nasal lacrimal intubation, and conjunctival dacryocystorhinostomy. In 37 patients, less than 5 mm of proximal canaliculus remained open. These patients were treated with conjunctival dacryocystorhinostomy alone, including four patients who had bilateral procedures. Two of 38 patients who underwent combined canalicular and conjunctival procedures required further surgery for a successful outcome compared with 14 of 37 patients who underwent conjunctival dacryocystorhinostomy without canalicular reconstruction (P = .002). Overall, 71 of 74 patients (96%) had a successful outcome, and five patients were lost to follow-up.

Jones pioneered the conjunctival dacryocystorhinostomy for the treatment of epiphora caused by canalicular obstruction.[1] In this procedure, a fistula is created between the conjunctiva and the nasal mucosa and obturated with a small glass tube. The success of the procedure depends on both the management of complications and ultimately the patient's motivation to be free of epiphora. Jones reported complete success with the procedure in a series of 500 patients.[2] The success rate reported by other investigators has been variable, which has caused some concern about the value of conjunctival dacryocystorhinostomy.[3]

Patients with distal canalicular obstruction can be treated with canaliculodacryocystorhinostomy to avoid committing them to a Jones tube. This procedure involves reconstructing the damaged canalicular segment, silicone elastic intubation of the nasal lacrimal system, and simultaneous dacryocystorhinostomy. This approach, however, is not reliable when the canalicular obstruction is proximal to the common canaliculus.[4,5] Under these circumstances, canalicular reconstruction is abandoned in favor of conjunctival dacryocystorhinostomy. Using a combined procedure of canalicular reconstruction and simultaneous conjunctival dacryocystorhinostomy, we attempted to salvage partially obstructed and stenotic canaliculi in patients for whom the probability of success with canaliculodacryocystorhinostomy would have been low. Patients with complete canalicular obstruction were treated with conjunctival dacryocystorhinostomy solely.

The surgical results of 79 consecutive conjunctival dacryocystorhinostomies performed over a 16-year period were reviewed. Thirty-eight patients underwent the procedure with concurrent canalicular reconstruction. Thirty-seven patients underwent conjunctival dacryocystorhinostomy without canalicular reconstruction, including four patients who had bilateral procedures.

Patients and Methods

Between April 1971 and June 1987, 79 consecutive conjunctival dacryocystorhinostomies were performed in 75 patients. Forty-four patients were females, and 31 were males. The mean age of the patients was 35 years and 44 years for the males and females, respectively.

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The age range was 6 to 80 years. The mean follow-up was 29 months (range, one to 123 months).

The causes of canalicular obstruction in this series included trauma (26 of 75 patients; 35%), inflammation (16 of 75 patients; 21%), tumors (ten of 75 patients; 13%), congenital anomalies (six of 75 patients; 8%), and idiopathy (17 of 75 patients; 23%) (Table). In males, trauma accounted for 18 of 31 cases (51%) and was the most common cause of canalicular obstruction. Inflammation was the most common cause of canalicular obstruction in females, accounting for 15 of 44 cases (34%). Tumors causing canalicular obstruction included resected basal cell carcinoma involving the medial canthus (five cases) and squamous papilloma of the lacrimal sac (four cases). One patient had canalicular obstruction after radiation therapy for a ciliary body melanoma.

All patients were seen by one of us (A.M.P.) and had a thorough lacrimal examination, which included a medical history, biomicroscopy, Schirmer I test, basic secretion test, dye retention test, and Jones primary and secondary dye tests.[6] Each canaliculus was probed with the 23-gauge tapered lacrimal needle used for the Jones secondary dye test. Dacryocystography was performed in some patients to clarify the nature of the obstruction.

Patients with epiphora because of internal scarring of the common canaliculus were initially treated with combined canalicular reconstruction, silicone elastic intubation, and dacryocystorhinostomy. Patients who were successfully treated in this fashion were excluded from this study. Nineteen of 75 patients had previously undergone dacryocystorhinostomy with silicone elastic intubation that failed. Patients with epiphora because of canalicular obstruction proximal to the common canaliculus or any form of canalicular obstruction after a dacryocystorhinostomy were treated in one of two ways. Patients with epiphora secondary to partial obstruction of the upper and lower canaliculi, or a single canaliculus, or paresis of the orbicularis oculi muscle, were treated with combined canalicular repair, nasal lacrimal intubation, and simultaneous conjunctival dacryocystorhinostomy. Overall, 17 of 38 patients treated with the combined procedure had undergone dacryocystorhinostomy that failed previously. One patient with common canalicular obstruction was treated with a primary combined canalicular reconstruction and conjunctival dacryocystorhinostomy because of the severity of medial canthal scarring. No attempt was made to reconstruct a canalicular system when less than 5 mm of both proximal canaliculi remained open. These patients were treated with conjunctival dacryocystorhinostomy solely.

TABLE
CAUSES OF CANALICULAR OBSTRUCTION

	FEMALE	MALE	TOTAL
No. of patients	44	31	75
Mean age (yrs)	44 (8–80)	35 (6–69)	41
Cause of canalicular obstruction			
Trauma	8	18	26
Tumor	7	3	10
Inflammation	15	1	16
Congenital anomalies	3	3	6
Idiopathy	11	6	17

When possible, surgery was performed with general anesthesia. Dacryocystorhinostomy was performed to the point of suturing the posterior lacrimal sac and nasal mucosal flaps.[7] When performed, canalicular reconstruction was then carried out by intubating stenotic canaliculi or excising abnormal portions of the canaliculi and suturing the remaining normal portions together over silicone elastic tubing. The caruncle was then excised, and an 18-gauge needle was guided from the bed of the caruncle to a point just anterior to the sutured posterior flaps. This tract was then enlarged with a No. 51 Beaver knife.

A Jones tube or a Putterman-Gladstone tube (a modified Jones tube) was inserted into the fistula. The Putterman-Gladstone tube has an extra flange that anchors the tube in the medial canthal soft tissues (Figure).[8] Middle turbinectomy was performed at the time of surgery if the middle turbinate interfered with tube placement. The tube was then sutured into place with 6-0 silk. The anterior nasal and lacrimal mucosal flaps were sutured together, and the overlying soft tissue was closed. (These procedures are described in more detail elsewhere.[9-11]) All operations were performed by one of us (A.M.P.).

To avoid clogging the lacrimal drainage tube, no ophthalmic ointments were used postoperatively, and a seven-day course of systemic antibiotics was prescribed. The skin sutures were removed six to ten days after surgery. Patency of the tube was tested initially by instilling saline solution into the palpebral cul-de-sac

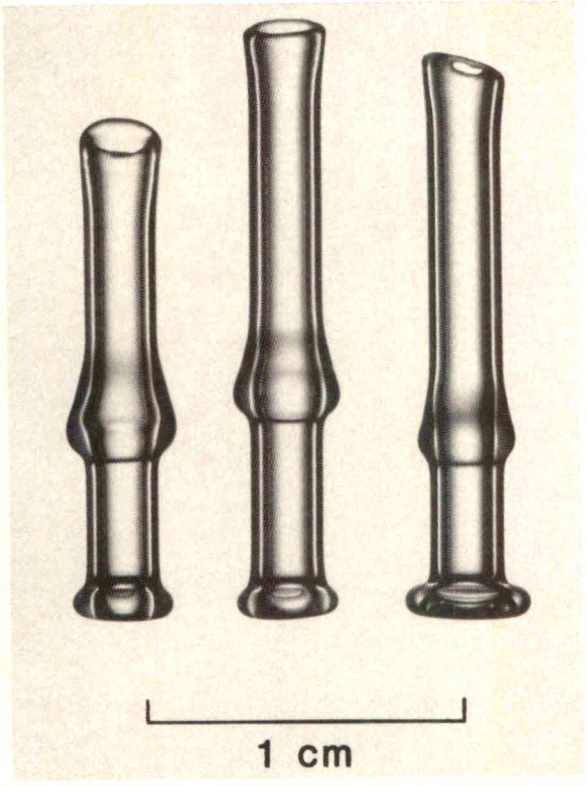

Figure (Steinsapir, Glatt, and Putterman). Putterman-Gladstone tubes of various sizes. The thick flange at the bottom of the modified Jones tube rests in the medial canthus. The middle flange anchors the tube in the medial canthal soft tissues.

while the patient occluded the contralateral nostril and inspired. With a functioning tube, saline was rapidly cleared through the tube. The tube was then irrigated with normal saline using a 23-gauge straight lacrimal needle to assess patency further and flush out any blood or mucus in the tube.

Three weeks postoperatively, the suture anchoring the lacrimal drainage tube to adjacent skin was removed. In those patients with combined canalicular reconstruction, the silicone elastic tube used to intubate the lacrimal system was left in place for three months. Four to six weeks after its removal, the canaliculi were probed and irrigated to assess patency.

Patients free of epiphora and discomfort were discharged to their referring ophthalmologists for routine care and asked to return for follow-up examinations every six to 12 months for tube cleaning. Patients were instructed to inspire saline eye wash through their tube twice daily to keep the tube clear of mucus. They were also told to close their eyelids and place a finger over the medial canthus before sneezing or nose blowing to prevent expelling the tube.

Results

A conjunctival dacryocystorhinostomy was defined as successful if a patient was comfortable, free of epiphora, and able to inspire fluid through the tube. Occasional episodes of epiphora related to mucus plugging of the tube or other types of reversible tube malfunction were considered compatible with a successful operation. A conjunctival dacryocystorhinostomy was defined as unsuccessful if a patient was uncomfortable, had epiphora, or was unable to inspire fluid through the tube. Fifty-five conjunctival dacryocystorhinostomies were successful after the initial surgery. Sixteen cases initially failed but were later successful after either revision of the conjunctival dacryocystorhinostomy or intranasal surgery. Two patients required two surgical revisions before the conjunctival dacryocystorhinostomy was successful. Five patients did not return for follow-up. Three patients with persistent epiphora after conjunctival dacryocystorhinostomy refused additional surgery, and those surgeries were therefore classified as failures. The overall success rate was 96% (71 of 74 patients) and was not dependent on canalicular reconstruction.

In 37 patients, 41 conjunctival dacryocystorhinostomies were performed without canalicular reconstruction. Four patients had bilateral procedures. Fourteen of these 37 patients (38%) required revision of the fistula or intranasal surgery to achieve a successful outcome. Thirty-eight patients had canalicular reconstruction at the time of conjunctival dacryocystorhinostomy. Two of these 38 patients (5%) required revision of the fistula or intranasal surgery to obtain a successful outcome. Data on the continued patency of the reconstructed canaliculi were available for 22 patients. In 18 of 22 patients, at least one canaliculus remained open four months after surgery (82%). The difference in the rate of surgical revision between patients who had conjunctival dacryocystorhinostomy with and without canalicular reconstruction (two of 38 patients vs 14 of 37 patients) was significant ($P = .002$, chi-squared test, one degree of freedom, Yates' continuity correction).

A standard Jones tube was used initially in all patients except in two in whom a Putterman-

Gladstone tube was used. Subsequently, 13 Jones tubes were replaced by Putterman-Gladstone tubes. Canalicular reconstruction had no effect on the type of tube used. Three of 13 patients had a Putterman-Gladstone tube placed during revision of the conjunctival dacryocystorhinostomy. An additional patient had a Putterman-Gladstone tube placed at the time of medial canthal horizontal shortening to help treat persistent epiphora. The remaining nine patients had simple replacement of their original Jones tube with a Putterman-Gladstone tube to treat tube extrusion and hypermobility. Clinically, the rate of tube complications in these patients was reduced.[12]

The complications of conjunctival dacryocystorhinostomy included extrusion (38 of 75 patients; 51%), obstruction (18 of 75 patients; 23%), medial migration (seven of 75 patients; 9%), malposition (seven of 75 patients; 9%), and hypermobility of the tube (three of 75 patients; 4%); granuloma formation (five of 75 patients; 7%); and infection (two of 75 patients; 3%).

The cause of complete or partial tube extrusion was not always determined, but in some patients it was related to rubbing of the eyelids, sneezing, or nose blowing. To minimize tube extrusion, patients were instructed to close the eyelids and place a finger over the medial canthus during these maneuvers. Tube extrusion was managed by reinsertion after tube cleaning. Complete extrusion of the tube for more than a few hours usually required dilation of the fistula to allow for tube reinsertion.[13] To prevent permanent closure of the fistula, the extruded tube was replaced as soon as possible. Permanent closure of the fistula occurred after tube extrusion in six patients. A second conjunctival dacryocystorhinostomy was performed in five of these patients. The sixth patient was free from epiphora after fistula closure because of successful canalicular reconstruction at the time of the original conjunctival dacryocystorhinostomy.

Recurrent tube extrusion was managed by placement of a smaller tube in four patients and by replacement of a Jones tube with a Putterman-Gladstone tube in eight patients. Six patients had recurrent tube extrusion because the Jones tube abutted the nasal septum or middle turbinate. Two patients required revision of the conjunctival dacryocystorhinostomy, nasal septoplasty, and middle turbinectomy. One of these patients later required a revision of the intranasal surgery. Two patients required revision of the conjunctival dacryocystorhinostomy and middle turbinectomy, and one patient required middle turbinectomy solely. None of these patients had middle turbinectomies at the time of their initial operation. The sixth patient required revision of the fistula.

Eighteen patients had one or more episodes of tube obstruction. Seventeen of 21 episodes resulted from mucus and cilia plugging the tube. These patients were treated by tube removal, cleaning, and reinsertion. The remaining four cases of obstruction were more complicated. One patient was found to have a metal foreign body lodged in the tube. In another patient, the tube was obstructed by a conjunctival symblepharon, which was excised. In one patient, the tube was resting on the middle turbinate. In the fourth patient, the tube was obstructed by a deviated septum and a nasal polyp. These last two patients also had tube extrusion, and their surgical treatment was described previously.

Medial migration occurred when the lacrimal drainage tube slipped into the fistula. Seven patients had this problem. In three patients, the problem was solved in the office by retrieving and repositioning the tube. In two other patients, the problem resolved after replacing the tube with a Putterman-Gladstone tube to manage recurrent tube extrusion. Revision of the conjunctival dacryocystorhinostomy was required in two patients; in one patient, the tube had migrated into the lacrimal sac.

Malposition occurred when the mouth of the tube was not aligned with the base of the lacus lacrimalis. This complication occurred in seven patients. In four patients, the tube contacted the globe in extreme adduction. In one patient, the tube was found to be resting on the middle turbinate, a situation that was relieved after middle turbinectomy. Three patients were treated by revision of the fistula. Two other patients received a smaller Jones tube. One patient insisted that the tube be removed despite being warned about the likelihood of recurrent epiphora.

Hypermobility occurred when the tube was in place in the fistula but could easily be displaced medially to laterally. This was often seen with tube extrusion. Isolated tube hypermobility occurred in three patients and was associated with inflammation of the tissues around the tube. The problem was managed in two of these patients by removal, cleaning, and reinsertion of the Jones tube. In the third patient, the hypermobility resolved when the

Jones tube was replaced with a Putterman-Gladstone tube.

Five patients developed granulomas adjacent to the Jones tube, which were treated by excision. In two patients, the granulomas partially obstructed the Jones tube. One patient reported a persistent foul odor. On examination, a granuloma was found abutting the tube. The odor resolved after the granuloma was excised.

Two patients developed infections related to their surgery. One patient developed a cellulitis at the site of the skin closure along the side of the nose. Culture of this site yielded *Staphylococcus aureus*. This patient responded well to antibiotic therapy, and the tube did not require removal. The second patient developed sinusitis on the side of the nose that underwent conjunctival dacryocystorhinostomy. This patient's infection was also treated without removing the Jones tube.

Discussion

R. D. Lisman, P. J. Silverstone, and B. Smith (oral communication, Nov. 8, 1989) questioned the value of the conjunctival dacryocystorhinostomy as a treatment of epiphora. They reported a success rate of less than 40% in a series of 102 patients who had conjunctival dacryocystorhinostomy performed by established surgeons (62 patients) and ophthalmology residents (40 patients). Their success rate was not consistent with the results of this study or other published studies.[2,3,14-18]

In 1976, Jones[2] reported that he had performed 500 conjunctival dacryocystorhinostomies with a 100% success rate, which reflected his willingness to repeat surgery until the tube functioned properly. Chandler[14] reported that in his series, 42 of 43 (97.7%) conjunctival dacryocystorhinostomies were successful. Weil[15] had a 93.5% success rate in a series of 178 conjunctival dacryocystorhinostomies. Lamping and Levine performed 40 conjunctival dacryocystorhinostomies.[16] Of the 35 patients who were followed up, 30 (86%) had a successful treatment outcome. Welham and Guthoff[17] reviewed their combined series of 204 Jones tube insertions. Follow-up was possible in 165 patients, and their success rate was 83%. Burger reported a 60% success rate in 50 consecutive cases.[3] Some of his patients experienced chronic irritation and conjunctivitis and asked to have their tubes removed. Nissen and Sorensen described 21 cases, of which only 12 (57%) were successful.[18] Only one of nine patients was willing to undergo surgery to replace a lost tube.

Jones[13] stated that once a fistula epithelialized and the surrounding granulation tissue contracted, the tube could be removed. However, he did not cite the number of his patients who maintained a patent fistula without a tube. Carroll and Beyer[19] designed a silicone rubber tube in the shape of the lacrimal drainage tract, which was used to obturate the fistula in 12 patients. Their goal was to encourage the development of an epithelialized tract that might function without a glass tube. At the end of an eight-month follow-up, five of 12 fistulas remained open. Two closed completely, and five required long-term dilatation. Campbell, Shannon, and Flanagan[20] used buccal mucosa to line the fistulas in their patients. Four of 11 patients had their Jones tubes removed after six months, and the fistulas remained patent at the end of a 10- to 13-month follow-up.

We believe that patients can learn to accept the tube. The possibility of a fistula closing is great, even years after the original surgery.[15] Reconstruction is expensive and exposes the patient to the risks of surgery and anesthesia. Consequently, we believe that the tube should be permanent, which is a view that is shared by a number of other authors.[3,15,21,22]

We performed canalicular reconstruction and conjunctival dacryocystorhinostomy simultaneously in 38 patients. These patients had distal obstruction or stenosis of the upper and lower canaliculus, or a single canaliculus, complete obstruction of the common canaliculus in the presence of extensive medial canthal scarring, or paresis of the orbicularis oculi muscle. Seventeen of these patients had previously undergone canalicular reconstruction that failed. All of these patients were believed to have a low probability of being free of epiphora if canalicular reconstruction alone were attempted. Canalicular salvage, therefore, was combined with simultaneous conjunctival dacryocystorhinostomy. Patients who had canaliculi salvaged at the time of conjunctival dacryocystorhinostomy were less likely to require further surgery for tube malfunctions than patients who had conjunctival dacryocystorhinostomy alone (two of 38 patients vs 14 of 37 patients; $P = .002$). Consequently, we believe that the combined procedure is an important alternative to abandoning the repair of remaining canalicular structures in selected patients. The reduced rate

of reoperation needed by these patients justifies the extra effort required to salvage the canaliculi at the time of conjunctival dacryocystorhinostomy. As a practical matter, the lacrimal drainage tube is never removed, even if the canaliculi are successfully reconstructed. Given the effort required to reconstruct the fistula and the risk of restenosis of the canaliculi, placement of the lacrimal drainage tube is considered permanent in this setting as well.

Hurwitz and Archer[5] advocate canaliculodacryocystorhinostomy as the treatment of epiphora caused by canalicular and common canalicular obstruction where at least 8 mm of proximal canaliculus remains open. We believe that this approach is only reliable for common canalicular obstruction not complicated by extensive medial canthal scarring. Success is much less likely when the obstruction involves individual canaliculi. Hurwitz and Rutherford[4] reported that five of ten patients with obstructions in the distal canaliculus underwent successful canaliculodacryocystorhinostomies. Whether a surgeon chooses to treat distal canalicular obstruction with canaliculodacryocystorhinostomy to avoid the placement of a permanent glass lacrimal drainage tube depends on the level of success achieved with the conjunctival dacryocystorhinostomy. Because we find the conjunctival dacryocystorhinostomy highly successful, it does not seem justified to subject a patient to an alternative operation that may succeed in only half of the cases. We believe that our combined procedure of canalicular reconstruction and conjunctival dacryocystorhinostomy is highly reliable and provides a better alternative to canaliculodacryocystorhinostomy in cases of distal canalicular obstruction.

The Putterman-Gladstone tube was introduced in 1984.[8] The extra flange securely anchors the tube in the soft tissues of the medial canthus. In this series, patients who had repeated episodes of tube extrusion and hypermobility with a Jones tube were nearly free of these problems after the insertion of a Putterman-Gladstone tube.[12] This tube is comfortable and appears to drain as well as a Jones tube. We now routinely use Putterman-Gladstone tubes at the time of conjunctival dacryocystorhinostomy. We believe that this tube will reduce the incidence of tube extrusion, which was 51% (38 of 75 patients) in this study.

The conjunctival dacryocystorhinostomy as a cure for epiphora represents a permanent commitment to a glass prosthesis. Presently, the patient cannot be promised that the fistula will remain open without the glass tube. Complications can occur at any time after surgery. Long-term, semiannual follow-up is, therefore, required. Patient motivation to be free of epiphora is essential for success. The ophthalmologist's experience in the diagnosis and management of postoperative complications is also critical.

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OPHTHALMIC MINIATURE

If Evelyn didn't recognise me straight away, it was because she was seeing me properly for the first time. She had just had her contact lenses fitted. She said that it was the most extraordinary experience she had ever had. The world was suddenly full of bright colours and defined shapes; things which people had spoken about for years and which she had never understood were suddenly clear to her. She spoke about her lenses the way most people spoke about LSD.

Frank Ronan, *The Men Who Loved Evelyn Cotton*
New York, Pantheon Books, 1989, p. 31

Immunohistochemical Analysis of Iris Biopsy Specimens From Patients With Fuchs' Heterochromic Cyclitis

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Using immunohistochemical techniques, we analyzed iris biopsy specimens from eight patients with Fuchs' heterochromic cyclitis, seven patients with various other types of uveitis, and eight glaucoma patients without uveitis. No specific abnormalities related to Fuchs' heterochromic cyclitis could be detected. Four of the patients with Fuchs' heterochromic cyclitis and four of the patients with uveitis showed evidence of an inflammatory cell infiltrate, which was a mixture of interleukin-2 receptor-negative T helper and suppressor cells, B lymphocytes, and plasma cells. Only an occasional T lymphocyte could be seen in two of the patients without uveitis. The class II antigen HLA-DR was expressed on iris stromal cells in every patient in the Fuchs' heterochromic cyclitis group and uveitis group and in six of the patients in the nonuveitis group. In six of the Fuchs' heterochromic cyclitis patients, including two without immunohistochemical evidence of inflammatory cell infiltrate, histologic abnormalities were present on hematoxylin and eosin sections.

VARIOUS HYPOTHESES have been proposed about the pathogenesis of Fuchs' heterochromic cyclitis.[1] Recent evidence suggests, however, that disturbances of the immunoregulatory system play an important role.[2-4] Quantitative examination of peripheral blood lymphocytes in Fuchs' heterochromic cyclitis[5] and other types of uveitis[5-7] is generally unhelpful because immune events occurring focally within the eye may not be reflected in peripheral blood lymphocyte profiles. Examination of intraocular fluids and tissues is essential, therefore, to gain an understanding of pathogenic mechanisms. Although results of light and electron microscopic examination of the iris in Fuchs' heterochromic cyclitis are well documented,[1,8-16] there have been no reports using immunohistochemical techniques. These techniques have been used, however, to study iris specimens obtained from patients with other chronic uveitis syndromes,[17-20] where T and B lymphocytes and increased expression of class II antigens have been found.

A slowly progressive B cell–mediated disease has been suggested as a pathogenic mechanism for Fuchs' heterochromic cyclitis[1] as a result of finding lymphocytes and plasma cells in the iris[1,8-16] and reduced T suppressor cell activity in the peripheral blood.[2] To gain a greater understanding of the immunopathogenic mechanisms involved, we performed an immunohistologic examination of iris biopsy specimens from patients with Fuchs' heterochromic cyclitis. We compared the results with those in patients without uveitis and patients with other types of uveitis.

Material and Methods

Iris biopsy specimens (from peripheral iridectomies) were obtained from eight patients (seven men and one woman, aged 23 to 54 years) with Fuchs' heterochromic cyclitis and

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seven patients (one man and six women, aged 59 to 77 years) with various other types of uveitis, classified according to the recommendations of the International Uveitis Study Group.[21] Diagnoses included idiopathic chronic anterior uveitis (three patients), panuveitis (three patients, two of whom had proven sarcoidosis), and idiopathic (HLA-B27–negative) recurrent anterior uveitis (one patient). Specimens were obtained either during extracapsular cataract extraction or trabeculectomy. At the time of surgery, no patients with Fuchs' heterochromic cyclitis were receiving systemic treatment, but two were using topical antiglaucoma preparations and two were using topical corticosteroid preparations. Two patients with uveitis were receiving systemic corticosteroids, four were using topical antiglaucoma preparations, and three were using topical corticosteroid preparations. Iris specimens were also obtained from eight patients without uveitis (two men and six women, aged 40 to 85 years) who had chronic simple glaucoma and were undergoing trabeculectomy. No patient received systemic therapy, and all patients were using topical antiglaucoma medication. Four of the patients had undergone argon laser trabeculoplasty in the year before surgery. We chose glaucoma patients, rather than patients undergoing extracapsular cataract extraction and intraocular lens implantation for senile cataract, for the group without uveitis because peripheral iridectomy is an integral part of trabeculectomy. All patients were informed about these investigations and their consent was obtained.

Specimens were snap-frozen in optimal cutting tissue compound within one hour of iridectomy. Cryostat sections of 6-μm thickness were air dried, fixed in acetone for ten minutes, and rinsed in phosphate-buffered saline, pH 7.4. Slides were then incubated for one hour at room temperature with a panel of monoclonal antibodies in phosphate-buffered saline containing 0.01% gelatin and 0.1% sodium azide. The antibodies used were as follows: as a pan T cell marker, we used antibodies against the CD2 (Dakopatts) and CD7 (Cell Biology Laboratory, Rotterdam) antigens. For the T helper and T suppresor/cytotoxic subset, antibodies against CD4 and CD8 markers were used (Becton Dickinson). Antibodies against the CD19 and CD20 antigens were applied to stain the B cells (Coulter Clone). Plasma cells were identified using separate antibodies against the immunoglobulin kappa and lambda light chains (Cell Biology Laboratory). Other markers included antibodies agains major histocompatibility complex class II antigens (Becton Dickinson) and the interleukin-2 receptor.

After rinsing in phosphate-buffered saline, slides were incubated for one hour at room temperature with peroxidase-conjugated polyclonal rabbit anti-mouse immunoglobulins (Dakopatts, Copenhagen, Denmark). Subsequently, slides were thoroughly washed in phosphate-buffered saline, and antigen-antibody binding was visualized using the substrate 3-amino-9-ethylcarbazole.[22] Sections were counterstained with Mayer's hematoxylin to obtain a discrete nuclear staining pattern. Positive reactions produced a red color, which made differentiation from dark brown endogenous melanin possible. Replacement of the primary antibody by phosphate-buffered saline served as a negative control. One slide from each specimen was stained with hematoxylin and eosin to evaluate the following pathologic features: focal depigmentation of iris pigment epithelium, hyalinization of vessel walls, iris stromal atrophy and fibrosis, and the disappearance of stromal melanocytes. One slide of each specimen was also stained with toluidine blue to detect mast cells.

Tissue sections were examined using 25× magnification by two independent observers (P.I.M. and C.M.M.), both of whom were unaware of the diagnosis. The scoring system described in the legend of Figure 1 was used.

Results

Immunohistologic findings for each group are summarized in Figure 1. No correlation could be seen between those patients receiving systemic or topical corticosteroid therapy, or both, and the presence or absence of any specific cell type.

In the Fuchs' heterochromic cyclitis group, four patients had a stromal infiltrate of CD2- or CD7-positive cells, or both, and of these there appeared to be an equal distribution of CD4- and CD8-positive cells (Fig. 2). Staining for the interleukin-2 receptor was negative for each patient. Although two patients showed scattered and clustered CD19- or CD20-positive cells, or both, in the iris stroma, kappa/lambda immunoglobulin G light chain staining on plasma cells was seen in three patients. This latter finding appeared to correlate well with the number of plasma cells seen on the correspond-

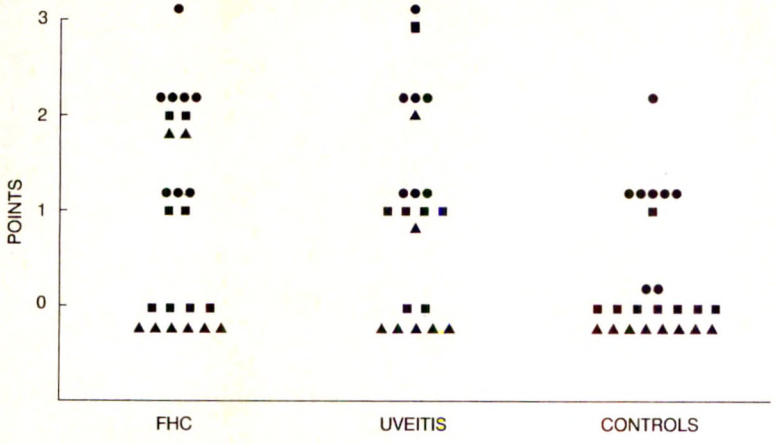

Fig. 1 (Murray and associates). Pan T cells (CD2/7 [squares]), B cells (CD19/20 [triangles]), and HLA-DR–positive cells (circles) in iris tissue from eight patients with Fuchs' heterochromic cyclitis, seven patients with uveitis, and eight patients with nonuveitic glaucoma (control patients). The following scoring system, which assessed positive staining cells from two sections, was used: 0 indicated zero to one cell; 1, few cells; 2, cells scattered or in small clusters; and 3, cells scattered and in clusters.

ing hematoxylin and eosin sections. Every patient had expression of the class II antigen HLA-DR, which was present on iris resident cells throughout the stroma, around the vessels, in the iris sphincter, and in the anterior cell border layer. Of the four patients without T or B lymphocyte infiltration, two showed histologically some evidence of focal depigmentation of the iris pigment epithelium, marked hyalinization of vessel walls, and iris stromal atrophy and fibrosis. Mast cells and a reduction in the number of stromal melanocytes were each found in three patients.

The findings in the patients with uveitis were similar to those in patients with Fuchs' heterochromic cyclitis. T and B cell markers were seen in four and two patients, respectively. HLA-DR–positive cells were also seen in every patient, and no patient was positive for the interleukin-2 receptor.

In the group of patients with glaucoma but not uveitis, only a few T cells, which were interleukin-2 receptor–negative, were seen in two patients. No B cells were identified. HLA-DR was expressed in six patients on single cells scattered throughout the stroma and in fewer numbers than in the other groups.

Discussion

No specific immunohistologic abnormalities in the irises of patients with Fuchs' heterochromic cyclitis were identified. We found no relationship between the various positive results in the same individual. The uveitis group also showed similar nonspecific staining results, which corresponds with those found in previous studies.[17-20]

Fuchs' heterochromic cyclitis has previously been described as an "intraocular B cell factory."[1] Many light and electron microscopic studies[1,8-16] that demonstrate a lymphocyte and plasma cell infiltrate in the iris support this description. In this study, however, a lymphocytic infiltrate was present in only one half of the patients examined, and plasma cells were present in three of eight patients. B lymphocytes were seen in only two of the three patients with plasma cells. This discrepancy can be explained because CD19 and CD20 molecules are expressed during the stages of B lymphocyte maturation but not on plasma cells.[23]

Despite the lack of immunohistologic evidence of T and B lymphocytes and plasma cells, characteristic findings of Fuchs' heterochromic cyclitis were present on hematoxylin and eosin sections in two patients. In one of these patients, local immunoglobulin G production and aqueous oligoclonal immunoglobulin G bands were demonstrated by isoelectric focusing and immunoblotting (unpublished data). This implies that there are clones of plasma cells present that were not detected by the methods used in this study, for which there may be two reasons; the small biopsy specimens obtained by peripheral iridectomy may not be representative of the whole iris, or immunoglobulin G is produced by plasma cells elsewhere in the eye.

Previous studies have demonstrated focal depigmentation of iris pigment epithelium, hyalinization of vessel walls, stromal atrophy and fibrosis, and reduced numbers of stromal melanocytes in the iris. Not all of these findings have been present, however, in every patient. In this study, evaluation of the possible loss of pigmented cells from the iris stroma was considered unreliable because we did not have a specimen of the opposite, normal iris for com-

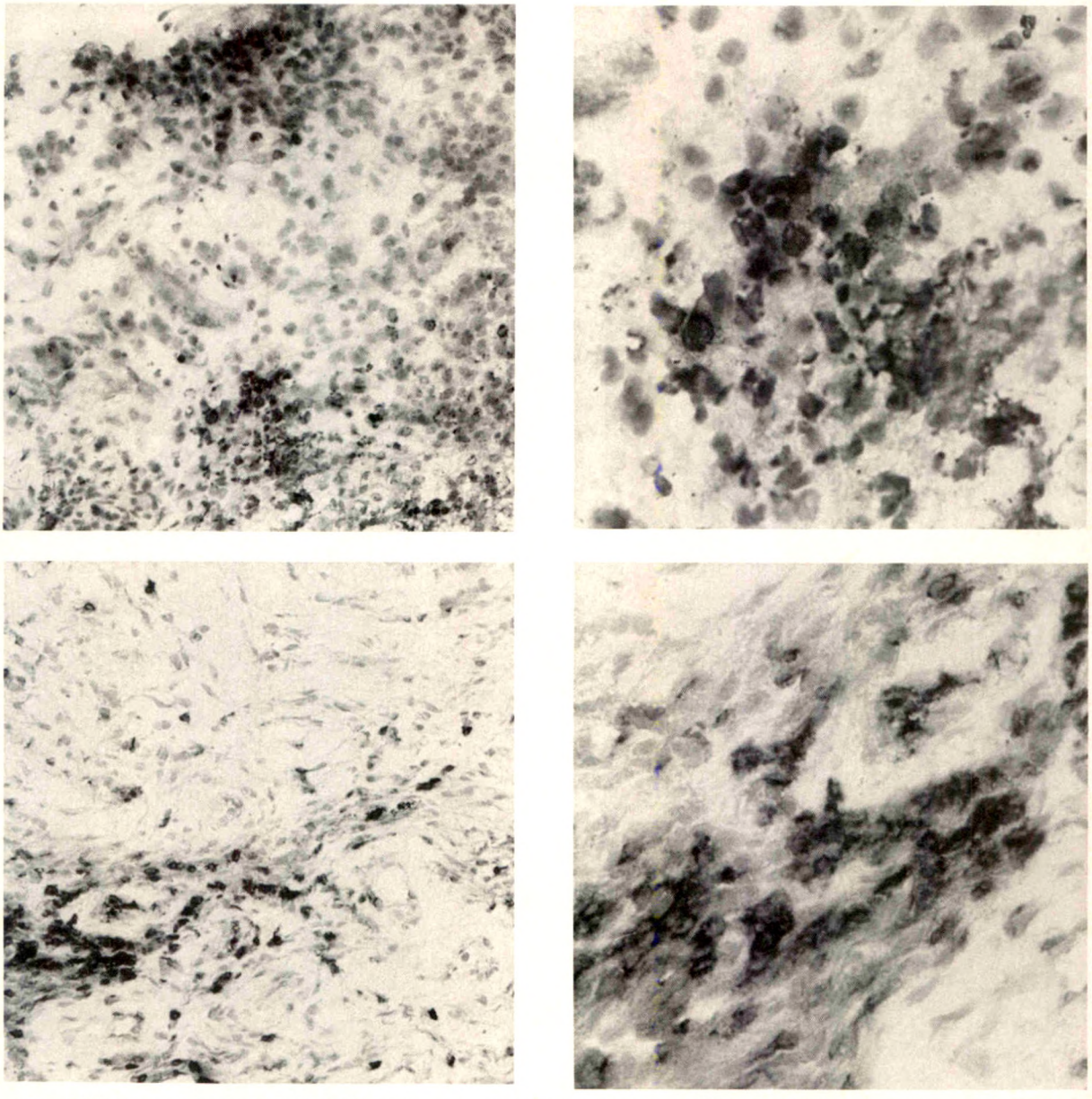

Fig. 2 (Murray and associates). Iridectomy specimen from a patient with Fuchs' heterochromic cyclitis (Patient 2). Top left, Clustered T cell (CD2-positive) infiltrate (×200). Top right, Higher magnification of a T cell (CD2-positive) cluster (×450). Bottom left, Scattered B cell (CD19-positive) infiltrate (×200). Bottom right, Higher magnification of this scattered B cell (CD19-positive) infiltrate (×450).

parison. Any loss, thinning, or irregularity of the iris pigment layer could have been attributable to artifact or surgical trauma. Also, hyalinization of vessel walls is known to occur to some degree in normal irises. Similarly, the demonstration of lymphocytes and plasma cells is a characteristic but not consistent finding in Fuchs' heterochromic cyclitis; a previous study[16] also failed to detect these cell types in some of their patients. It may be that the histologic appearance depends on the chronicity of the disease, and those patients who have had the disease for longer will show more abnormalities. This appears not to be the case in this study, because the two patients who failed to show any abnormality on immunohistochemical and hematoxylin and eosin staining had their condition diagnosed many years earlier

than some patients with characteristic histologic abnormalities. This inconsistency may also be attributable to the size of the specimen examined, because most of the previous histologic studies[8-12,14,15] were performed on whole globes and on specimens from sector iridectomies rather peripheral iridectomies.

The enhanced expression of HLA-DR on iris resident cells in the Fuchs' heterochromic cyclitis and uveitis groups may indicate a state of immunologic responsiveness,[24] but the T lymphocytes seen in the four patients in each of these groups all appeared to be nonactivated because they were interleukin-2 receptor–negative. The class II antigen expression may be involved, therefore, in the perpetuation of the disease process. Mast cells may also play a role in the pathogenesis of some types of uveitis,[25] but the increased number of mast cells previously reported in Fuchs' heterochromic cyclitis[16] could not be confirmed.

The absence of any notable lymphocytic infiltrate and the presence of HLA-DR in the glaucoma group without uveitis corresponds to findings in previous studies,[18,19] but the exact figures for those patients with chronic simple glaucoma were not given. Expression of class II antigens in the normal iris has also been reported by others,[26] although some have refuted this observation.[20,27,28] Previous work has shown a mild inflammatory reaction in the irises of animals that have undergone argon laser trabeculoplasty.[29] In this study, none of the four glaucoma patients without uveitis previously subjected to laser therapy showed any immunohistologic evidence of an inflammatory infiltrate.

Immunohistochemical analysis of iris biopsy specimens in Fuchs' heterochromic cyclitis failed to show any specific immunohistologic abnormality in what is a supposed uniform condition. Perhaps the classification of diseases based on clinical methods alone does not necessarily relate to the disease's pathologic findings. It is conceivable, therefore, that Fuchs' heterochromic cyclitis may be a single clinical entity with more than one histologic and pathologic mechanism.

ACKNOWLEDGMENTS

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OPHTHALMIC MINIATURE

His uncle, on the other hand, developed a hoarse dry nervous cough and lapsed into almost total wordlessness. His eyes turned to pools behind the rimless glasses; the white and dark of the sockets blurred, became indistinguishable. Their sole light seemed to come from the occasional sudden flarings in the sun or in the fires of the furnace.

Chaim Potok, *The Book of Lights*
New York, Fawcett Crest, 1981, p. 5

Acute Scleritis in Porphyria Cutanea Tarda

John F. Salmon, F.R.C.S. Edin., Paul C. Strauss, M. Med., Gail Todd, Ph.D., and Anthony D. N. Murray, F.R.C.S. Edin.

We examined three patients who had dermatologic and biochemical manifestations of porphyria cutanea tarda and localized thinning or excavation in the sun-exposed interpalpebral sclera, adjacent to the cornea. All three patients had signs of acute scleritis. The acute scleritis responded to oral indomethacin in one patient, but systemic corticosteroids were required to control the inflammation in the other two patients. Phlebotomy, protection from sunlight, and refraining from alcohol played an important part in the treatment of the patients.

PORPHYRIA CUTANEA TARDA is the most common disorder of porphyrin-heme metabolism seen in Europe and America. In southern Africa, the disease occurs primarily in Blacks [1-3] This predominantly dermatologic disease is characterized clinically by cutaneous photosensitivity, formation of bullae, an increase in skin fragility, hyperpigmentation, hypertrichosis, and sclerodermoid changes.[4] It is distinguished biochemically by increased hepatic synthesis and urinary excretion of excessive amounts of uroporphyrin and smaller amounts of 7-carboxylporphyrin and coproporphyrin. The ocular features of this disease are uncommon, and few descriptions of active scleral involvement exist. The predisposing cause of the porphyria in these patients was probably excessive alcohol consumption over many years.

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Case Reports

Case 1

A 69-year-old black woman was referred for examination because of a painful left eye and reduced vision in both eyes. She had a long history of bilateral, intermittent, ocular pain and complained of recurrent blistering of the hands and feet. For many years she had ingested large quantities of home-brewed, traditional, tribal beer.

On examination, the best-corrected visual acuity was R.E.: 20/30 and L.E.: 20/200. The right eye had small areas of nasal and temporal scleral thinning, limited to the interpalpebral region (Fig. 1). Small, white, old keratic precipitates were present in an inferior distribution. The eye was otherwise normal. The left eye had signs of acute diffuse anterior scleritis, limited to the nasal sclera. Circumferential scleral transparency, typical of previous anterior scleritis, was present. A small semicircular excavation was present nasally, in the anterior interpalpebral sclera. An active, nongranulomatous, anterior uveitis was noted. Posterior synechiae

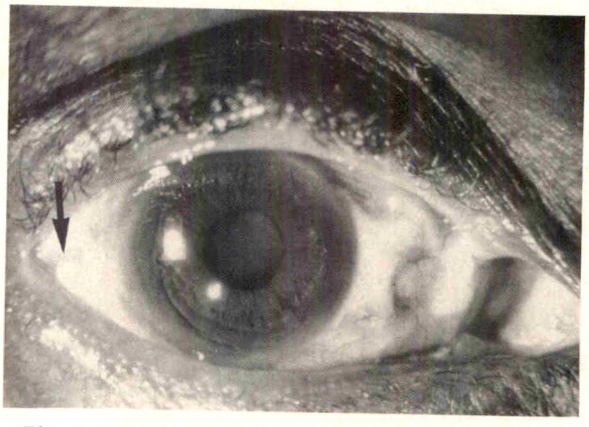

Fig. 1 (Salmon and associates). Case 1. Right eye shows nasal scleral thinning and temporal excavation (arrow) in the interpalpebral region.

and a posterior subcapsular cataract prevented examination of the fundus. Ultrasound examination disclosed a normal posterior segment.

On systemic examination, the patient had sclerodermalike changes of the skin. Resorption of the terminal phalanges was present. Active blistering, ulceration, and scarring of the hands and feet were noted. She had patchy scalp alopecia, with facial and forearm hypertrichosis. No signs of rheumatoid arthritis or other collagen-vascular disease were found.

A urine uroporphyrin level of 1,170 nmol/l supported the clinical diagnosis of porphyria cutanea tarda (Table). A ferritin level of 555 μg/l suggested an increase in stored iron.

Topical prednisolone four times daily and 1% atropine drops twice daily, combined with 25 mg of oral indomethacin three times daily, were commenced. The ocular inflammation diminished within six days. From then on, the patient refrained from alcohol consumption and avoided exposure to sunlight. On three occasions in a four-month period, 500 ml of whole blood was removed. Three months after her initial examination, she had another episode of acute scleritis, which was controlled within one week with oral indomethacin. The blistering of the skin stopped, and she had no further cutaneous ulceration after the third phlebotomy. The urinary porphyrin levels were significantly reduced (Table). Eighteen months later, both eyes were free of pain without treatment, but the areas of scleral thinning and transparency remained unchanged (Fig. 2).

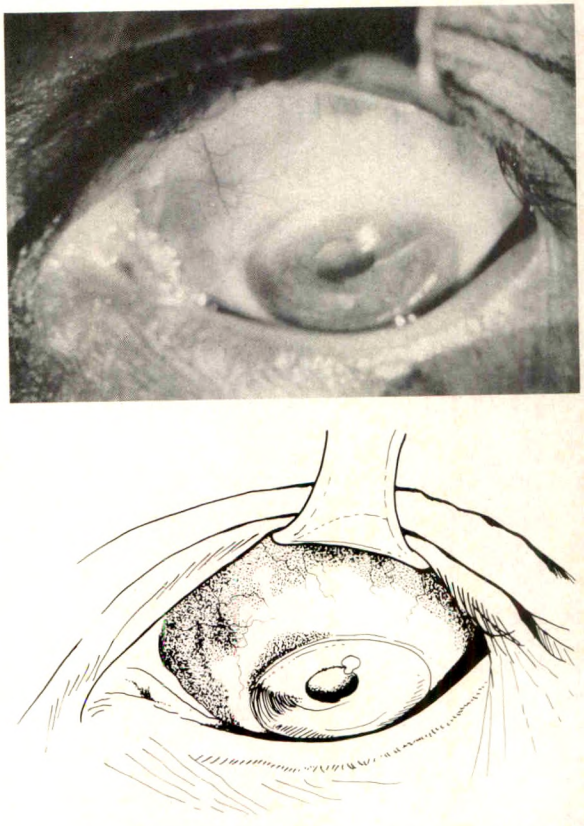

Fig. 2 (Salmon and associates). Case 1. Top, Left eye on depression shows circumferential scleral transparency typical of previous acute scleritis. Bottom, Circumferential scleral transparency shown in shaded area.

Case 2

A 66-year-old black man had a three-week history of severe pain in the left eye. The pain kept him awake at night and was not relieved by oral analgesics. He had not suffered from previous ocular disease. Recurrent blistering and increased fragility of the skin of his hands had

TABLE
URINARY PORPHYRIN ASSAYS

	NORMAL LEVEL	PATIENT 1		PATIENT 2*	PATIENT 3	
		INITIAL	AFTER THERAPY	INITIAL	INITIAL	AFTER THERAPY
Uroporphyrin	<20 nmol/l	1,170 nmol/l	34 nmol/l	2,118 nmol/l	1,044 nmol/l	224 nmol/l
7-carboxyl-porphyrin	<1.5 nmol/l	1,018 nmol/l	15.2 nmol/l	2,327 nmol/l	1,088 nmol/l	224 nmol/l
6-carboxyl-porphyrin	0 nmol/l	187 nmol/l	0 nmol/l	1,542 nmol/l	468 nmol/l	80.6 nmol/l
5-carboxyl-porphyrin	0 nmol/l	215 nmol/l	0 nmol/l	1,241 nmol/l	579 nmol/l	102 nmol/l
Coproporphyrin	<240 nmol/l	130 nmol/l	8.4 nmol/l	1,265 nmol/l	535 nmol/l	86.1 nmol/l
Aminolevulinic acid	<45 μmol/l	17.8 μmol/l	0 μmol/l	42.3 μmol/l	25.6 μmol/l	22.9 μmol/l
Porphobilinogen	<16 μmol/l	2.8 μmol/l	0 μmol/l	12.8 μmol/l	5.8 μmol/l	2.3 μmol/l
Creatinine	10 mmol/l	6.1 mmol/l	4 mmol/l	26.7 mmol/l	16.6 mmol/l	6.1 mmol/l

*Patient 2 died.

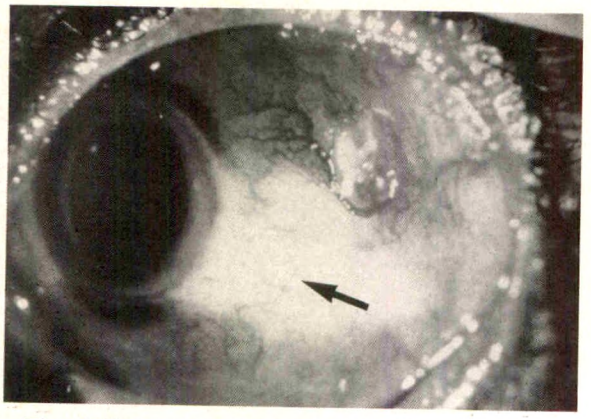

Fig. 3 (Salmon and associates). Case 2. Left eye shows an oval area of scleral thinning in the interpalpebral region (arrow). Diffuse scleral inflammation is present above and below this area.

been present for several years. He had a history of chronic alcohol abuse.

On examination, the visual acuity was 20/20 in each eye. The right eye was normal. In the temporal sclera of the left eye, an oval area of scleral resorption and thinning measuring 7 × 3 mm was present. Diffuse scleral inflammation above and below this area was noted (Fig. 3). There were signs of an acute anterior uveitis. The fundus was normal.

Scars and hyperpigmentation were present on the dorsum of the patient's hands and other areas exposed to the sun. No active skin lesions were noted. On systemic examination, there was no evidence of diseases usually associated with scleritis, and no signs of rheumatoid arthritis were apparent. The unique isomeric pattern of porphyrins in the urine, and a uroporphyrin level of 2,118 nmol/l, confirmed the diagnosis of porphyria cutanea tarda (Table). Hepatomegaly and abnormal liver function test results compatible with alcoholic liver disease were demonstrated.

Topical prednisolone acetate four times daily and 25 mg of oral indomethacin three times daily were commenced. Five days later, the patient reported a sudden increase in pain and marked visual loss in the left eye. On examination, the visual acuity was reduced to 3/200. He had signs of acute diffuse scleritis with a large temporal exudative retinal detachment, which extended into the macular region. There was evidence of cellular activity in the anterior chamber and anterior vitreous. A daily oral dose of 60 mg of prednisone was added, and after eight days the visual acuity improved to 20/40. The detachment was significantly smaller, and peripheral, flame-shaped hemorrhages could be observed in the temporal retina. The eye continued to improve, and the prednisone was reduced over a three-week period. When treatment was stopped, a small area of temporal scleral thinning remained, without signs of scleral inflammation.

Two months later, the patient was readmitted to the hospital with end-stage liver failure. Both eyes were free of pain, and no inflammation was present. In addition to biochemical evidence of chronic liver disease, the presence of an underlying primary hepatocellular carcinoma was suggested by an alpha-fetoprotein level of 550 ng/l (normal, 2 to 10 ng/l). The patient died two days after admission. A postmortem examination was not performed.

Case 3

A 59-year-old man had a two-week history of pain in the right eye. During the previous two years, the patient had experienced intermittent, severe pain in both eyes. Recurrent blistering and increased fragility of the skin of the hands had been present for 30 years. The patient had a long history of excessive alcohol consumption. He had received a complete course of treatment for pulmonary tuberculosis the year before examination.

On examination, the best-corrected visual acuity in each eye was 20/40. Both eyes had a small area of scleral thinning in the nasal interpalpebral region and early nuclear sclerosis (Fig. 4). A small, semicircular excavation was

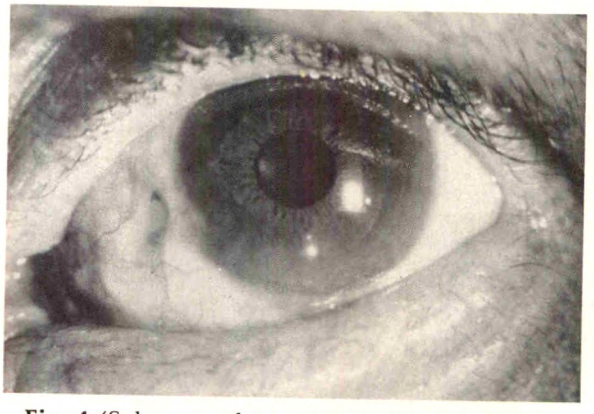

Fig. 4 (Salmon and associates). Case 3. Left eye shows an area of scleral thinning adjacent to the cornea.

visible in the temporal sclera of the right eye associated with diffuse anterior scleritis above and below this area. Examination through a dilated fundus disclosed a peripheral area of temporal exudative choroidal detachment.

Systemic examination disclosed scars on the sun-exposed areas of the patient's hands, face, and neck. No active vesicles or bullae were present. He had patchy scalp alopecia and facial hypertrichosis. Prominent onycholysis was present. There were no signs of tuberculosis, rheumatoid arthritis, or systemic lupus erythematosus. A soft, diffusely enlarged liver was palpated.

Laboratory investigations confirmed the clinical diagnosis of porphyria cutanea tarda (Table). The serum ferritin level was exceptionally high (1,103 μg/l) and the patient had biochemical evidence of abnormal liver function. Serologic testing showed antinuclear antibody at a dilution of 1:20. Rheumatoid factor was not detected. The sputum was negative for acid-fast and alcohol-fast bacilli. A liver biopsy specimen showed the typical features of alcoholic hepatitis.

Topical prednisolone four times daily and 25 mg of oral indomethacin three times daily were commenced. After two weeks on this regimen, the scleritis had not improved. An intravenous infusion of 500 mg of methylprednisolone dissolved in 100 ml of 5% dextrose solution was then administered over 30 minutes. By the next day, the eye was free of pain and subsequently became less inflamed, and the exudative choroidal detachment settled. The infusion of methylprednisolone was repeated three times over the following two weeks. Four weeks after the initial examination, a phlebotomy was performed and 500 ml of whole blood was removed.

The eye remained free of pain for four weeks while the patient was taking 10 mg of prednisone, 25 mg of indomethacin, and 300 mg of isoniazid daily. Soon after stopping this therapy, he experienced another episode of acute diffuse inflammation in the nasal sclera of the right eye (Fig. 5). The scleritis was controlled by recommencing oral indomethacin and by using 30 mg of prednisone daily for one week. A phlebotomy was repeated. At his last visit, the patient was asymptomatic on 25 mg of oral indomethacin three times daily. The urine porphyrin levels were reduced after the second phlebotomy (Table).

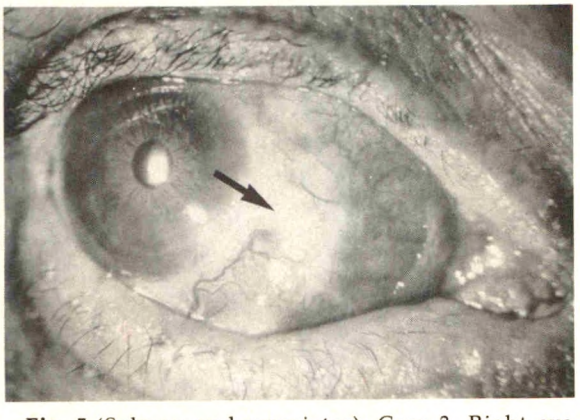

Fig. 5 (Salmon and associates). Case 3. Right eye shows acute diffuse scleritis nasally above and below a white area of scleral avascularity and thinning (arrow).

Discussion

The porphyrias are a group of diseases in which abnormalities in the porphyrin-heme metabolic pathway occur. They have been divided into two major types: erythropoietic and hepatic.[5] Porphyria cutanea tarda, first described by Waldenström in 1937, is a hepatic porphyria.[6] Decreased activity of uroporphyrinogen decarboxylase, an enzyme in the heme biosynthetic pathway, leads to overproduction and excessive storage of porphyrins in the liver.[7] Primarily uroporphyrin, but also 7-carboxyl-porphyrin and coproporphyrin, are released into the circulation and are excreted in the urine and feces. Porphyrins, which are highly photoactive chromophores, are deposited in the dermis and absorb radiant energy, predominantly in the wavelengths near 400 nm. It has been proposed that the photoexcited porphyrin molecules precipitate a localized biochemical reaction, which may result in the formation of hydrogen peroxide and lipid peroxides.[8] The peroxides appear to cause cellular and lysosomal membrane disruption with the release of hydrolytic enzymes, which subsequently results in tissue damage.[9]

Although the disease may be inherited in an autosomal dominant manner, a family history is usually not obtained.[7] Other factors that play an important role in the pathogenesis of porphyria cutanea tarda are excessive alcohol consumption, iron overload, estrogen therapy, or

exposure to chlorinated hydrocarbons.[4,10] In all three of our patients, the major predisposing factor appeared to be alcohol abuse over many years. Two patients had biochemical evidence of an excessive serum iron concentration, which is a characteristic finding in porphyria cutanea tarda.[11] The precise role of iron in the pathogenesis of the disease is unclear, but the increase in the quantity of iron in the body stores is probably caused by excessive absorption of iron through the gastrointestinal tract.[11] One patient had a marked increase of the serum alpha-fetoprotein concentration, suggesting the possibility of an underlying hepatocellular carcinoma. Although this diagnosis was not confirmed histologically, the cutaneous changes of porphyria cutanea tarda have been previously described as a rare manifestation of hepatic tumors.[12,13] It has also been suggested that the development of a sudden exacerbation of dermatologic signs in a patient with longstanding porphyria cutanea tarda may be caused by a hepatic malignancy.[13]

These three patients demonstrate the range of cutaneous manifestations seen in this disease.[1-4] Rarely is the eye damaged in porphyria cutanea tarda, and most of the previously described ocular abnormalities have occurred in the areas of the eye and adnexa that are exposed to the sun. The following conditions have been reported[14-17]: cicatricial ectropion with symblepharon formation; lacrimal duct obstruction; blepharochalasis; congestion, edema, and hyaloid thickening of the conjunctiva; corneal scarring; and scleral disease.

Scleral involvement is a rare complication of congenital erythropoietic porphyria and of two of the adult forms of porphyria: porphyria variegata and porphyria cutanea tarda.[15,18] The scleral changes in porphyria cutanea tarda were first reported as painless, bilateral, symmetric areas of scleral thinning.[19] In a subsequent authoritative description of the ocular manifestations of porphyria, Barnes and Boshoff[15] described the scleral lesions in greater detail. Although the types of porphyria were not specified, six of their 84 patients had localized areas of scleral excavation and none had signs of acute scleritis. They suggested that scleral penetration occurred rapidly, was seldom complete, and was not restricted to the sclera alone, but spread over the corneoscleral limbus to encroach onto the cornea. The conjunctiva, which reformed over the lesions where open ulcerations had occurred, showed linear streaks of scar tissue.

Sevel and Burger[16] described a 51-year-old man with porphyria cutanea tarda who had reduced vision in one eye and no light perception in the other. The eyelids were scarred, but no ectropion was present. Both eyes had marked conjunctival hyperemia and congestion. A triangular area of scleral thinning was present in both eyes, within the interpalpebral fissures, close to the cornea. The area was white and had the appearance of a senile hyaline plaque. Both corneas were scarred, and a localized descemetocele was present next to the corneoscleral limbus in the blind eye. This eye was enucleated, and histologic examination disclosed chronic inflammatory cells in the subconjunctival tissue, but no evidence of necrogranulomatous scleritis.

Chumbley[17] described two cases of confirmed porphyria cutanea tarda with bilateral scleral involvement. Localized areas of scleral resorption and thinning, with exposure of the uveal pigment, were found next to the cornea. One eye had an area of scleral inflammation stretching from the corneoscleral limbus to the fornix. The scleritis progressed to involve the temporal half of the globe anteriorly, and despite oral corticosteroids, it spread to involve the entire anterior aspect of the globe. After three months of intensive topical, subconjunctival, and systemic corticosteroids, the scleritis subsided, but the areas of scleral thinning persisted. Five years after the initial examination, the patient was re-examined and was found to have phthisis bulbi.

The relatively high incidence of porphyria in southern Africa, a delay in seeking medical therapy for cutaneous manifestations, and excessive exposure to sunlight may explain the preponderance of ocular cases of porphyria cutanea tarda.

Our three patients had the typical scleral lesions previously associated with porphyria cutanea tarda. The sclera was thinned or excavated over a sharply demarcated area, with a bluish color in the base. This area was located in the sun-exposed interpalpebral region, adjacent to the cornea. Additionally, all three patients had signs of acute diffuse anterior scleritis. Two patients had signs of posterior scleritis, one of whom had an exudative retinal detachment and the other of whom had a peripheral choroidal detachment.[20] Two of the three pa-

tients had signs of acute anterior uveitis, a complication that may be found in 30% of all eyes with scleritis.[21]

The pathogenesis of the scleral complications is unknown, but presumably ocular damage and cutaneous damage are caused by similar mechanisms. Photosensitivity caused by excessive porphyrins may play a major role in the development of ocular damage. Sevel and Burger,[16] using thin-layer chromatographic analysis, demonstrated uroporphyrin and 7-carboxylporphyrin in conjunctival and scleral tissue. Their histologic findings suggest that the porphyrins cause vesication in the exposed parts of the conjunctiva with subsequent scarring. Firm adherence of the conjunctiva to the underlying sclera causes dehydration of the sclera, which then manifests clinically as an area of thinning.

The factor that precipitated the acute scleritis in all three of our patients, who had suffered from porphyria for many years, remains unknown. No patient had clinical or laboratory evidence of rheumatoid arthritis or other systemic disease normally associated with scleritis. An association with systemic lupus erythematosus has been noted in porphyria cutanea tarda, and although a low titer of antinuclear antibody was detected in the serum of one of our patients, no other evidence of collagen-vascular disease was found.[22]

In the treatment of these patients, consideration should be given to both the general treatment of porphyria and to the specific treatment of acute scleritis. Treatment should begin with the elimination of any predisposing factors, and patients should abstain from alcohol consumption. Patients should also avoid sunlight. The safest and most effective treatment for the cutaneous manifestations of porphyria cutanea tarda is phlebotomy.[4,23] The usual method is to remove 500 ml of blood every one to three weeks for periods ranging from two to ten months. A total of 2 to 10 l of blood is removed.[9] Clinical improvement normally begins within three to six months, and the procedure should be repeated until the hemoglobin is reduced to 10 to 11 g/100 ml. Biochemical remission may not occur until more than seven months after clinical remission.[4] This intensive approach was precluded in one of our patients because of the seriousness of the underlying liver disease, and in the other two patients it was precluded because of poor patient compliance regarding outpatient follow-up. Chloroquine or hydroxychloroquine therapy has been reported to be useful in patients with porphyria cutanea tarda, but was not used in our patients.[24,25] Because hydroxychloroquine is as effective and is less likely to produce retinopathy than chloroquine, it should be considered the drug of choice when this method of therapy is used.[25]

Our experience in treating acute scleritis associated with porphyria cutanea tarda suggests that indomethacin is useful for mild forms of acute anterior scleritis, but that systemic corticosteroids should be used for severe scleritis, particularly if there is posterior segment involvement. Either oral prednisone or intravenous injections of high doses of methylprednisolone appear to be equally effective. The intermittent administration of methylprednisolone treatment has been shown to be remarkably successful in controlling severe destructive scleral disease, but is usually reserved for patients who are resistant to conventional therapy.[26] We used this approach in a patient who had a history of tuberculosis to avoid prolonged use of oral prednisone. Although this therapy can produce long-term remissions, it may be hazardous and sudden death has been reported during or after the infusion.[26,27] The pain relief and reduction of inflammation was dramatic in our patient, and no side effects were noted. Oral prednisone was required in a low dose afterward to control the scleritis.

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Serologic Tests in the Diagnosis of Presumed Toxoplasmic Retinochoroiditis

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We treated three patients who had documented *Toxoplasma* retinochoroiditis and negative immunofluorescent antibody toxoplasmosis titers (titer < 1:16), positive Sabin-Feldman dye titers of 1:64, 1:16, and 1:64 in the three patients, respectively, and a positive enzyme-linked immunoassay titer of 1:256 in the one patient tested. In patients with negative immunofluorescent antibody toxoplasmosis titers, we recommend obtaining Sabin-Feldman or enzyme-linked immunoassay titers, or both, before excluding the diagnosis of ocular toxoplasmosis.

THE DEFINITIVE DIAGNOSIS of ocular toxoplasmosis requires the demonstration of the proliferative form of *Toxoplasma gondii* in ocular tissues.[1] *Toxoplasma* retinochoroiditis is, therefore, usually a presumptive diagnosis based on a compatible lesion in the fundus and positive serologic results for *Toxoplasma* antibodies. Additionally, other causes of focal exudative retinitis, including syphilis, tuberculosis, sarcoidosis, cytomegalovirus, and fungal infections must be excluded.[2]

Although the Sabin-Feldman dye test represents the standard against which all other tests are measured, it is no longer routinely performed. The indirect immunofluorescent antibody test, which has largely replaced the Sabin-Feldman dye test, is believed to be as sensitive and specific. The three cases of toxoplasmic retinochoroiditis described herein demonstrate the limitations of current serologic testing using the indirect immunofluorescent antibody test.

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Material and Methods

A commercially available indirect immunofluorescence assay (Fiax test kit Toxo-G Antibodies, Whittaker M.A. Bioproducts, Walkersville, Md.) was used by the serology laboratory at The Presbyterian Hospital of New York. Accuracy of the test kit is validated using quality control samples provided in each kit. To maximize specificity, testing begins with a serum dilution of 1:16 (maximum concentration). A Fiax titer of less than 16, therefore, indicates that no detectable antibodies are present.

The Sabin-Feldman dye test was performed by the serology laboratory at Cornell Hospital with the Feldman and Lamb modification of the Sabin-Feldman *Toxoplasma* dye test.[3] Both positive and negative controls are assayed simultaneously in each run to ensure sensitivity and specificity.

A commercially available enzyme-linked immunoassay test (Abbott Toxo-G Eia kit, Abbott Laboratories, North Chicago, Ill.) was used by the serology laboratory at The Presbyterian Hospital of New York. Accuracy is validated by using quality control samples provided in each kit.

Case Reports

Case 1

A 52-year-old man had decreased visual acuity in his right eye for one week. Visual acuity was R.E.: counting fingers and L.E.: 20/20. The corneas were clear, and there were no keratic precipitates. The right anterior chamber contained many cells and dense flare. Fundus examination of the right eye disclosed a macular chorioretinal scar and a satellite exudative retinal lesion temporal to the macular scar with a moderate number of inflammatory cells in the vitreous (Fig. 1). A chest x-ray disclosed no

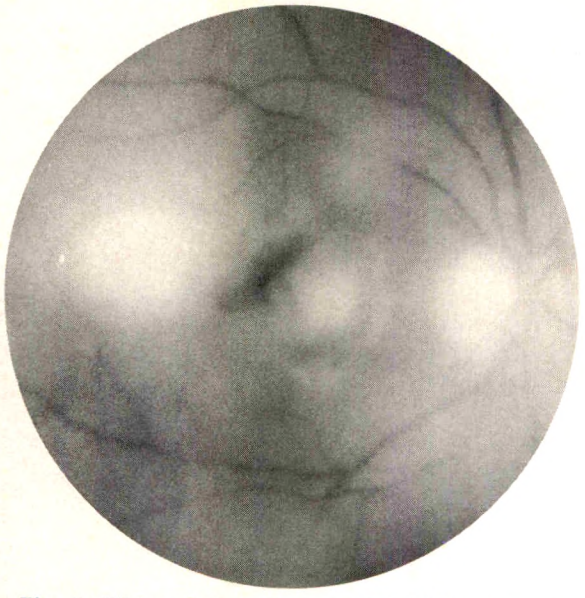

Fig. 1 (Weiss, Velazquez, and Hofeldt). Case 1. Macular chorioretinal scar and a satellite exudative retinal lesion temporal to the scar with a moderate vitritis.

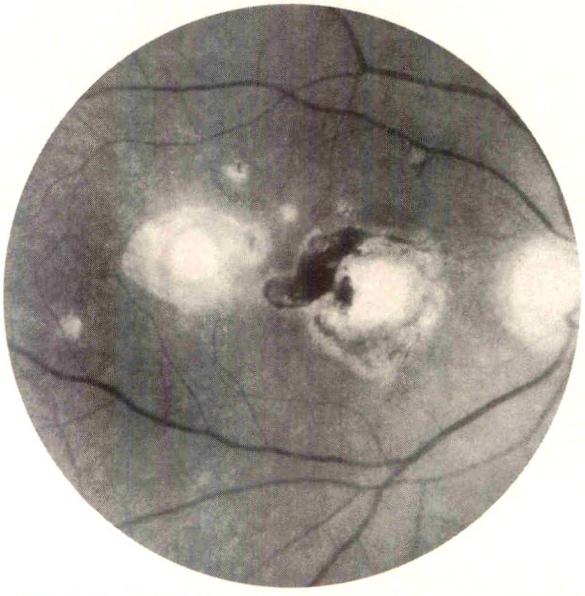

Fig. 2 (Weiss, Velazquez, and Hofeldt). Case 1. The vitritis has markedly decreased in the fourth week of therapy.

abnormalities, and VDRL-fluorescent treponemal antibody and intermediate purified protein derivative (5 tuberculin units) were negative. Results of an indirect immunofluorescent antibody test for *Toxoplasma* species was negative (titer < 1:16). Results of the Sabin-Feldman dye test were positive with a titer of 1:64. The patient was started on the following regimen: 1 g of trisulfapyrimidine four times daily, 25 mg of pyrimethamine twice daily (after an initial dose of 100 mg), 3 mg of folinic acid three times weekly, and 20 mg of prednisone three times daily. The patient responded well to therapy with resolution of the uveitis (Fig. 2). Therapy was continued for six weeks with gradual tapering of the prednisone. His visual acuity improved to 20/400, and the patient has remained asymptomatic during 1½ years of follow-up.

Case 2

A 13-year-old boy with a history of poor vision in his left eye since birth had blurred vision in his right eye for three days. Visual acuity was R.E.: 20/60 and L.E.: counting fingers. Results of slit-lamp examination were noncontributory. Ophthalmoscopic examination disclosed chorioretinal scars in the inferonasal and superotemporal quadrants of the right eye. Additionally, an inferotemporal parafoveal retinitis was seen with moderate cells in the vitreous overlying the lesion (Fig. 3). A large inactive macular chorioretinal scar was present in the left eye (Fig. 3). A chest x-ray disclosed no abnormalities, and VDRL-fluorescent treponemal antibody titers and intermediate purified protein derivative (5 tuberculin units) were negative. An indirect immunofluorescent antibody for *Toxoplasma* species was negative (titer < 1:16). Results of the Sabin-Feldman dye test were positive with a titer of 1:16. The patient was treated with 1 g of trisulfapyrimidine three times daily, 25 mg of pyrimethamine twice daily (after an initial dose of 75 mg), 3 mg of folinic acid three times weekly, and 20 mg of prednisone three times daily. Within three weeks of therapy, the patient's visual acuity in his right eye improved to 20/20 (Fig. 4). Therapy was continued for six weeks, with gradual tapering of the prednisone. The patient remains asymptomatic after one year of follow-up.

Case 3

A 17-year-old boy had blurred vision in his right eye for five days. He could not recall any previous visual difficulties; however, he had been told by an ophthalmologist that he had a retinal scar in his right eye. His general health was good, and his medical history was noncontributory. Visual acuity was R.E.: counting fingers and L.E.: 20/20. Results of slit-lamp exam-

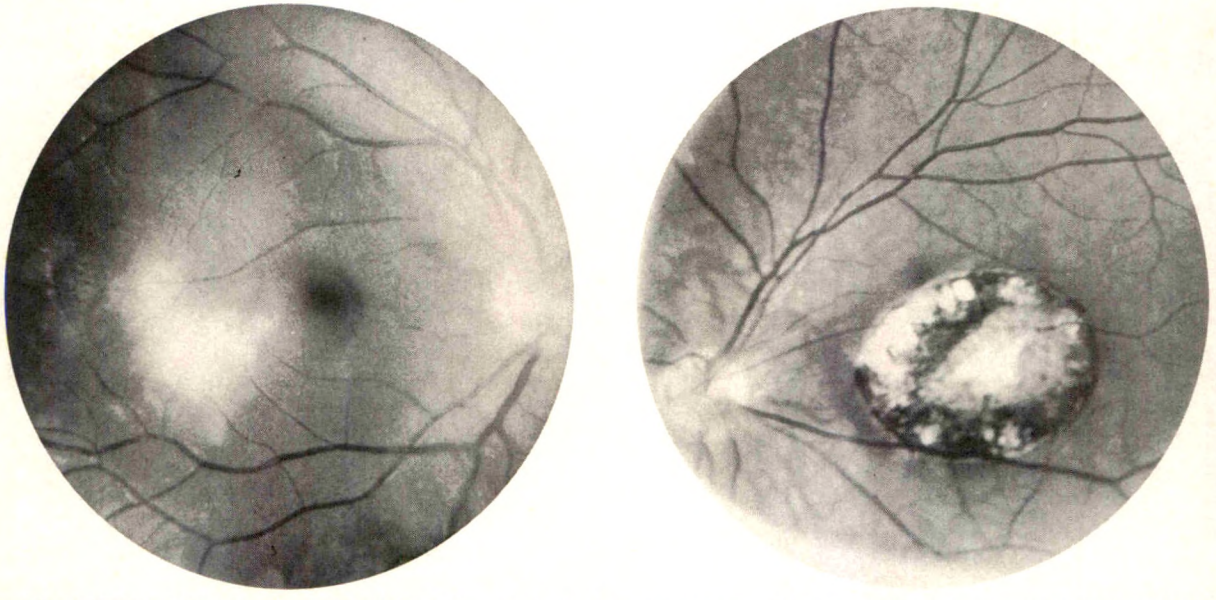

Fig. 3 (Weiss, Velazquez, and Hofeldt). Case 2. Left, Punctate inner retinitis with minimal vitritis in the right eye. Right, Macular scar in the left eye.

ination were normal. Fundus examination of the right eye disclosed a serous detachment of the sensory retina involving the macula and surrounding arcades with a yellow-white retinal lesion in the inferonasal position of the macula (Fig. 5). There were only trace inflammatory cells in the vitreous. Examination disclosed that the left eye was normal. It was believed that the fundus lesion represented outer punctate toxoplasmosis, and the patient was started on the following regimen: 1 g of

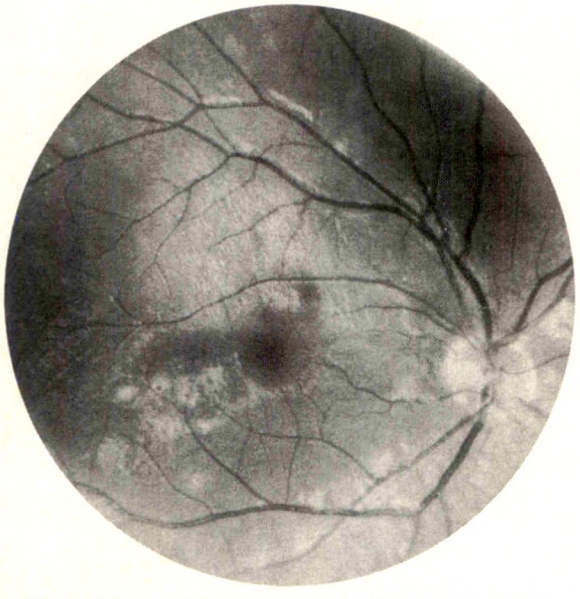

Fig. 4 (Weiss, Velazquez, and Hofeldt). Case 2. The retinitis appeared inactive within three weeks of initiating therapy.

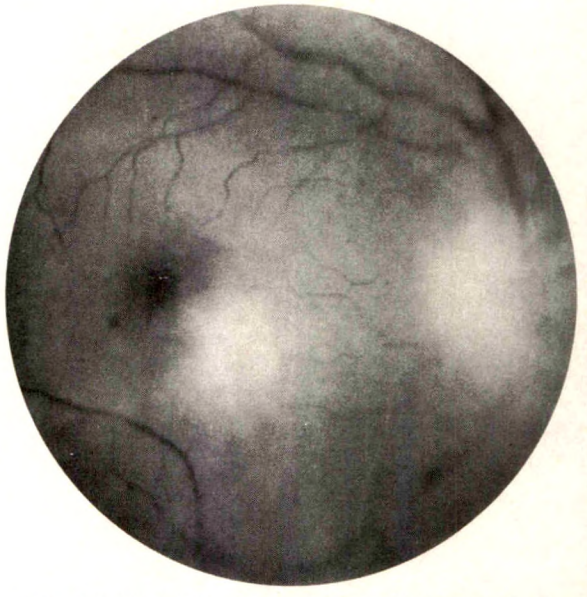

Fig. 5 (Weiss, Velazquez, and Hofeldt). Case 3. Five days after the onset of blurred vision. Note the exudative retinal lesion with indistinct borders, the serous detachment of the macula, and the indistinct optic disk margins.

sulfadiazine four times daily (after an initial dose of 4 g), 300 mg of clindamycin four times daily, and 20 mg of prednisone three times daily.

Initial laboratory studies, including VDRL, fluorescent treponemal antibody absorption test, indirect immunofluorescent antibody for toxoplasmosis, and enzyme-linked immunoassay for *Toxocara* species were negative. A chest x-ray disclosed no abnormalities. An intermediate purified protein derivative was positive, but the patient had received bacillus Calmette-Guerin vaccine. Subsequently, the Sabin-Feldman dye test and the enzyme-linked immunoassay for *Toxoplasma* were both positive (1:64 and 1:256, respectively).

Within two weeks of initiating therapy, the serous retinal detachment resolved. The borders of the retinal lesion became more distinctly outlined, and retinal edema decreased. The patient's visual acuity improved to 20/400 in his right eye. The antibiotic therapy was continued for six weeks with gradual tapering of the prednisone. The patient's visual acuity in his right eye has remained 20/400, and there has not been a recurrence during one year of follow-up.

Discussion

Establishing the presence of antitoxoplasmic antibody in a patient's serum is considered essential to the diagnosis of *Toxoplasma* retinochoroiditis, especially in cases where clinical features are unusual and a characteristic fundus lesion is lacking (as in Case 3). Any titer of antibody is significant because in recurrent ocular toxoplasmosis, no correlation exits between the level of *Toxoplasma* titers and activity of the ocular disease.[4]

The immunofluorescent antibody test has been the most widely used test for the detection of antitoxoplasma, IgG, or IgM antibodies.[5] Although it is relatively easy to perform, the interpretation of results can be misleading. False-negative IgM titers may occur because of competitive inhibition by simultaneously present antitoxoplasmic IgG.[6] False-positive IgM titers have occurred because of the presence of rheumatoid factor.[7,8] This occurs because rheumatoid factor (which is an IgM anti-IgG) can bind to specific antitoxoplasmic IgG. These false reactions can be eliminated by using gel filtration to separate IgM from IgG antibodies before testing, or preabsorbtion of serum with a preparation containing staphylocci and streptococci, which eliminates nonspecific IgM reactions by removing all IgG.[8,9] Finally, the presence of antinuclear antibodies in a patient's serum may cause false-positive IgM and IgG antitoxoplasmosis titers.[10] This may occur because toxoplasmic organisms contain antigens indistinguishable by immunologic techniques from those found in human leukocyte nuclei. Because IgM titers in ocular toxoplasmosis are only significant for diagnosing the rare case of acquired retinochoroiditis,[11,12] the specificity limitations of the immunofluorescent antibody test are virtually restricted to false-positive IgG titers because of the presence of antinuclear antibodies.

The double sandwich enzyme-linked immunoassay test for antitoxoplasma antibodies eliminates IgM specificity problems associated with the immunofluorescent antibody test.[13,14] False-positive reactions owing to rheumatoid factor and false-negatives because of competing IgG are avoided because only IgM of the test serum adheres to plates precoated with anti-IgM antiserum. The enzyme-linked immunoassay test for *Toxoplasma* antibodies is believed to be as specific and sensitive as the Sabin-Feldman dye test.[4]

Despite the limitations of immunofluorescent antibody testing specificity, it has been considered to be as sensitive as the Sabin-Feldman dye test. The latter test is now rarely used because it requires the constant maintenance of virulent organisms in the laboratory with associated risk to laboratory personnel.

In the three cases of *Toxoplasma* retinochoroiditis, the immunofluorescent antibody IgG titers were negative despite a positive Sabin-Feldman dye test. In Case 3, antitoxoplasmosis titers using the enzyme-linked immunoassay test were found to be positive at 1:256. Commercially available immunofluorescent antibody tests for *Toxoplasma* antibodies begin testing with a 1:16 serum dilution (maximum concentration) because specificity decreases when more concentrated serum dilutions are used. Thus, it is reasonable to anticipate a significant percentage of false-negative titers because any titer of antibody, even in undiluted serum, is considered significant in establishing the diagnosis of toxoplasmic retinochoroiditis. We cannot explain the apparent lack of relative sensitivity of the immunofluorescent antibody

test performed in our laboratory. Maximum Sabin-Feldman dye test titers were recorded at 1:64 in Patients 1 and 3. Because immunofluorescent antibody titer testing began at a 1:16 dilution, a greater than fourfold increase in the sensitivity of the Sabin-Feldman dye test would be needed to explain the negative (< 1:16) immunofluorescent antibody titers obtained.

In cases of suspected ocular toxoplasmosis with negative immunofluorescent titers, we recommend obtaining a Sabin-Feldman titer or enzyme-linked immunoassay titer, or both, before excluding the diagnosis of ocular toxoplasmosis.

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Adjunctive Use of Delayed and Adjustable Low-Dose 5-Fluorouracil in Refractory Glaucoma

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We used delayed 5-mg subconjunctival injections of 5-fluorouracil as an adjunct to filtering surgery in ten eyes with refractory glaucoma. The first 5-fluorouracil injection was made three to 15 days postoperatively and was used only when clinical signs suggested an impending bleb failure. These signs included flattening and localization of bleb, increased vascularity, early subconjunctival scarring, loss of microcystic conjunctival changes, and increased intraocular pressure. After a follow-up of ten to 17 months (mean, 13.7 months), an intraocular pressure of less than 21 mm Hg was attained in five eyes without medication and in four eyes with medication. The treatment failed in one eye. The average dose of 5-fluorouracil was 28 ± 12 mg per eye. There were no conjunctival wound leaks. Six eyes developed transient corneal epithelial defects. The modified administration of 5-fluorouracil can result in fewer conjunctival wound leaks. Its use can be limited to those patients who show evidence of impending bleb failure.

PATIENTS with refractory glaucomas and those in whom previous ocular surgery has been performed are at risk for failure of subsequent filtration surgery.[1-4] Recent studies describing the use of 5-fluorouracil as an adjuvant therapy to filtration surgery have shown promising results in these patients.[5-8] It is recommended that the subconjunctival injection of 5-fluorouracil be made at the conclusion of the operation and daily for two weeks thereafter.[6] This schedule, however, is associated with conjunctival wound leaks and corneal epithelial defects.[6,7-11]

Careful observation of filtration blebs has indicated that bleb failure is preceded by clinical signs that occur three or more days after surgery. Therefore, we used a variable schedule: initiation of therapy at least three days after surgery to minimize early conjunctival wound leaks; subconjunctival injection of 5-fluorouracil 90 to 180 degrees from the filtration site; and titrating the frequency of 5-mg 5-fluorouracil injections according to the clinical signs suggesting bleb failure. We used our variable schedule in ten consecutive patients with refractory glaucoma who had signs of early bleb failure.

Material and Methods

Ten eyes of ten patients with advanced refractory glaucoma were included in this study (Table 1). Nine of the ten eyes had undergone at least one previous intraocular surgical procedure. The remaining eye had Axenfeld-Rieger syndrome with advanced glaucoma. Eight of the ten eyes had undergone at least one unsuccessful filtration procedure, two eyes had undergone Nd:YAG laser trabeculopuncture, one eye had undergone Nd:YAG laser to a failed filtering sclerostomy, one eye had undergone cyclocryotherapy, and one eye had undergone 360-degree buckling for retinal detachment. Three eyes were pseudophakic, and two eyes were aphakic.

After local or general anesthesia was induced, the conjunctiva was grasped in the fornix with nontoothed forceps, and the superior (or inferior) rectus muscle was grasped with St. Martin toothed forceps deep in the superior (or

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TABLE 1
DEMOGRAPHIC AND CLINICAL DATA

PATIENT NO., AGE (YRS), SEX, RACE	DIAGNOSIS	PREVIOUS OPERATIONS	INTRAOCULAR PRESSURE (MM HG)		VISUAL ACUITY		FOLLOW-UP (MOS)
			PREOPERATIVE	POSTOPERATIVE	PREOPERATIVE	POSTOPERATIVE	
1, 71, M, W	Primary open-angle glaucoma	Extracapsular cataract extraction and posterior chamber intraocular lens and trabeculectomy	25	17	20/100	20/80	14
2, 62, F, W	Chronic angle-closure glaucoma	Trabeculectomy	47	16*	20/100	20/70	14
3, 39, M, B	Juvenile glaucoma	360° buckling operation; posterior lip sclerectomy; Nd:YAG laser trabeculopuncture	26	17	20/200	20/80	12
4, 73, M, W	Primary open-angle glaucoma	Extracapsular cataract extraction and posterior chamber intraocular lens and trabeculectomy	18	7	20/25	20/40	15
5, 79, M, W	Primary open-angle glaucoma	Trabeculectomy; extracapsular cataract extraction; argon laser trabeculoplasty (1 wk before filtration surgery)	50	16	20/400	20/70	17
6, 17, F, W	Corticosteroid-induced glaucoma	Posterior lip sclerectomy; Nd:YAG laser trabeculopuncture	30	10	20/30	20/30	16
7, 24, F, W	Angle-recession glaucoma after corneoscleral laceration	Repair laceration; pars plana lensectomy; cyclocryotherapy	49	36†	CF‡ 2 ft	20/400	15
8, 76, F, W	Pseudoexfoliation glaucoma	Posterior lip sclerectomy; extracapsular cataract extraction and anterior vitrectomy and anterior chamber intraocular lens; Nd:YAG laser to sclerostomy	74	12	CF 6 ft	20/70	12
9, 42, F, W	Chronic angle-closure glaucoma	Laser iridotomy (×2), posterior lip sclerectomy	45	13	20/25	20/25	12
10, 29, M, W	Axenfeld-Rieger syndrome	—	35	9	20/25	20/20	10

*After cataract extraction and vitrectomy.
†Intraocular pressure was 19 mm Hg after YAG transscleral cycloablation and maximum tolerated medical therapy.
‡Counting fingers.

inferior) fornix. This permitted incision in the overlying redundant conjunctiva, which ensured a wound distant from the sclerostomy site. A 4-0 bridle silk suture was placed with a noncutting needle. The conjunctival incision was made with a Westcott scissors. A broad

tenonectomy was performed unless excessive bleeding occurred. The corneoscleral limbus was exposed by using blunt dissection with a cotton-tipped applicator and a No. 15 Bard-Parker blade. Bipolar diathermy controlled bleeding. A paracentesis was performed by using a disposable Wheeler knife, and its patency was confirmed with the injection of balanced salt solution through a No. 30 disposable needle.

When a trabeculectomy was performed, a triangular 4 × 4-mm half scleral thickness flap was made. After the sclerostomy, it was loosely closed with a single 10-0 nylon suture at the apex. When posterior lip sclerectomy was performed, the anterior chamber was entered with a No. 75 blade, and a Kelly-Descemet punch was used to perform the sclerostomy. A basal iridectomy was performed with care to ensure that the pillars fell outside of the margins of the sclerostomy. The conjunctiva was closed with a continuous 9-0 or 10-0 nylon suture. Posterior Tenon's tissue was included in the closure to provide a posteriorly directed vector on the conjunctival incision. At the end of the procedure, subconjunctival gentamicin and dexamethasone were injected 180 degrees from the sclerostomy. Topical atropine 1%, erythromycin, and dexamethasone ointments were applied to the eye, and a patch and shield were applied.

As long as the filtration bleb looked functional, no 5-fluorouracil was given. Signs of an actively filtering bleb included low intraocular pressure, elevated bleb with minimal vascular infiltration, diffuse bleb, and microcystic conjunctival changes. When impending bleb failure was suspected, 5-fluorouracil was administered subconjunctivally using a single dose of 5 mg no greater than 90 degrees away from the edge of the bleb. The clinical signs of impending bleb failure included the following: increased vascularization of bleb; flattening of bleb; decrease of conjunctival microcystic changes; signs of subconjunctival fibrosis (including localization of bleb; migration of suture-line towards corneoscleral limbus in limbal-base flap operation, and direct vascularization of subconjunctival fibrous tissue); and a trend toward increased intraocular pressure. Not all of the signs of failure were present in an eye, and often the earliest signs of bleb failure were noted while the intraocular pressure was low. Patients were seen daily after administration of 5-fluorouracil, and the need for additional injection was determined on the basis of signs of bleb failure or detection of side effects, such as conjunctival wound leaks, corneal erosions, and flattening of the anterior chamber.

In order to compare our data with those of other investigators using 5-fluorouracil, similar definitions of surgical outcome were adopted.[6,12] A complete success was defined as an intraocular pressure of less than 21 mm Hg without medication. A qualified success was defined as an intraocular pressure of 22 to 25 mm Hg without medication or less than 22 mm Hg using medication. A qualified failure was an intraocular pressure more than 25 mm Hg without medication or an intraocular pressure more than 21 mm Hg with medication. Complete failure was defined as further glaucoma surgery or loss of light perception.

Results

The patients included five men and five women who ranged in age from 17 to 79 years (mean, 51.2 ± 23.5 years). The follow-up was ten to 17 months (mean, 13.7 months). The filtration surgery was successful in nine eyes. Five eyes were considered complete successes, and four eyes were considered qualified successes. There was only one failure (Patient 7). Intraocular pressure before surgery ranged from 18 to 74 mm Hg (mean, 39.9 ± 16.4 mm Hg). Postoperatively, intraocular pressure ranged from 7 to 36 mm Hg (mean, 15.3 ± 18.1 mm Hg). Visual acuity decreased by one to two lines of the Snellen chart in one patient, whereas in seven patients visual acuity improved by one to two lines. Visual acuity was unchanged in two patients.

The total dose of 5-fluorouracil per eye ranged from 10 to 50 mg (mean, 28 ± 12.2 mg). The number of injections per eye ranged from two to ten (mean, 4.6 ± 2.4). The time interval between surgery and the first 5-fluorouracil injection ranged from three to 15 days postoperatively (mean, 7.7 ± 4.1 days). The interval between surgery and the final injection of 5-fluorouracil ranged from eight to 26 days postoperatively (mean, 17 ± 6.1 days). Good control of intraocular pressure in all nine eyes was associated with an elevated, diffuse bleb, de-

TABLE 2
PATIENT RESPONSE TO 5-FLUOROURACIL

PATIENT NO.	CLINICAL SIGNS OF BLEB FAILURE	ADMINISTRATION OF 5-FLUOROURACIL, FIRST TO LAST INJECTION (POSTOPERATIVE DAYS)	NO. OF INJECTIONS (TOTAL DOSE [MG])	CLINICAL RESPONSE		SURGICAL OUTCOME
				FINAL OUTCOME	COMPLICATIONS	
1	Intraocular pressure rose to 23 mm Hg, thick vascular flattened bleb	6 to 18	4 (20)	Elevated bleb, microcystic changes, persistent subconjunctival scar tissue	Subconjunctival hemorrhage	Qualified success
2	Low thick bleb, decrease of microcystic changes	9 to 16	6 (30)	Quiet, elevated bleb and microcystic changes	Persistent corneal epithelial defect, malignant glaucoma, pars plana vitrectomy	Qualified success
3	Injected bleb, scarring adjacent to sclerostomy	3 to 9	7 (35)	Quiet, elevated bleb still thickened; microcystic changes	Superficial punctate keratitis, persistent corneal epithelial defect	Qualified success
4	Loss of microcysts, flattened bleb, beginning of subconjunctival scarring	15 to 20	2 (10)	Microcysts redeveloped, elevated cystic bleb, no further progression of fibrosis	Subconjunctival hemorrhage	Complete success
5	Increased vascularity of bleb, flattening of bleb, shift of suture line toward corneoscleral limbus	14 to 21	7 (35)	Elevated bleb, microcystic changes	Corneal abrasion	Complete success
6	Increased vascularity of bleb, flattening of bleb, shift of suture line toward corneoscleral limbus	6 to 20	7 (35)	Elevated, diffuse, cystic bleb	Corneal abrasion	Complete success
7	Injected bleb, increased vascularity of bleb, sterile hypopyon	5 to 22	6 (30)	Flat and vascular bleb	Conjunctival wound gap, negative Seidel test, corneal abrasion	Failure
8	Injected, flattened bleb	3 to 8	5 (25)	180°, quiet, elevated bleb with microcystic changes	–	Qualified success
9	Increased vascularity of bleb, loss of microcystic changes	7 to 10	2 (10)	Increased microcystic changes, bleb more diffuse nasally	–	Complete success
10	Increased vascularity of bleb, localization of bleb	9 to 26	10 (50)	Diffuse, vascular bleb with microcystic changes	Corneal abrasion	Complete success

creased vascularity of bleb, and increase of microcystic conjunctival changes. In the one eye that failed, the filtering bleb was flat and vascular (Table 2).

There were no conjunctival wound leaks in any eye that underwent filtration surgery. In Patient 7, whose treatment failed, a conjunctival wound gap was detected, but there was no aqueous humor leak, and results of repeated Seidel tests were negative. The anterior chamber remained deep in this patient. In three eyes, subconjunctival hemorrhage occurred immediately after the injection. These resolved within ten days. Six eyes had corneal epithelial defects. In four eyes, these defects were transient, and re-epithelialization occurred within days. In two eyes (Patients 2 and 3), the corneal abrasion persisted for one month and required the application of a therapeutic soft contact lens. All six eyes that developed corneal epithelial defects received a total dose of 30 mg of 5-fluorouracil or more (a mean dose of 38 mg of 5-fluorouracil per eye compared with a mean dose of 16 mg of 5-fluorouracil in the four eyes that did not develop corneal complications).

Discussion

In these ten consecutive patients, a variable schedule of 5-fluorouracil administration was used in an attempt to reverse impending filtration failure. In nine of the ten patients, the signs of impending bleb failure disappeared, and the patients achieved long-term control (mean, 13.7 months) of intraocular pressure associated with the development of functional filtration.

Previous studies of subconjunctival fibrosis and filtration surgery failure[13-15] have indicated that the wound healing process is staged. In a study describing the time course of cellular proliferation after experimental glaucoma filtration surgery, Jampel and associates[16] demonstrated, by tritiated thymidine autoradiography, that fibroblasts at the scleral wound edge and subconjunctiva reached the peak of their proliferative activity three to five days postoperatively. Because cellular proliferation immediately precedes a sharp rise of intraocular pressure, this event in the healing process is believed to play an important role in the failure of filtration blebs. Because 5-fluorouracil predominantly inhibits the proliferative process, it is expected to be more efficient in doing so at this stage of maximal fibroblastic replication. Clinical support comes from the observation that the signs of impending filtration failure tend to be delayed by a number of days. Consequently, we believe this supports the rationale for delaying the administration of 5-fluorouracil after surgery.

In a study of subconjunctival injections of 5-fluorouracil after filtration surgery, Rockwood and associates[17] reported a success rate of 68% in aphakic eyes and 82% in eyes with previously failed filtering surgery within one year. The two-year success rate was 63% and 75%, respectively.[17] Other studies have confirmed the benefit of 5-fluorouracil in refractory glaucoma patients.[8,12] Results of studies suggest that although 5-fluorouracil helps control the subconjunctival fibrotic response, the antimetabolic activity of 5-fluorouracil is commonly associated with complications such as corneal epithelial defects and conjunctival wound leaks.[6,7,9-12,17]

The current dosage regimen recommended by the 5-Fluorouracil Study Group is 10 mg of 5-fluorouracil daily in the first postoperative week followed by 5 mg per day in the second postoperative week. Using this regimen, Heuer, Parrish, and Gressel[6,7] reported an incidence of 36% to 41% for conjunctival leaks and 45% to 50% for corneal epithelial defects. Weinreb[12] successfully reduced these complications by adjusting the 5-fluorouracil dosage according to clinical findings, although the injection at the completion of surgery was retained. In 24% of the eyes treated, conjunctival wound leaks were noted, whereas 29% had corneal epithelial defects.

Early conjunctival wound leaks are frequently associated with flattening of the bleb and a high failure rate, which serves as another reason for delaying 5-fluorouracil administration. In an attempt to promote the closure of the conjunctival incision, the initiation of 5-fluorouracil therapy was delayed in our study by a minimum of 72 hours, and in eight of the ten eyes treatment was delayed for more than five days. Because the conjunctival wound was allowed to heal, we adopted a more aggressive approach to the injection of 5-fluorouracil. Typically, the injection site was 90 degrees from the sclerostomy site unless the bleb extended to the proposed site of injection. In the latter case,

the injection was made close to the bleb edge, but the area of active filtration was avoided. (Other investigators have recommended that the injection be made 180 degrees away from the bleb.[6]) We adopted this modification in an effort to increase the concentration of 5-fluorouracil at the filter site, although we have no scientific evidence that this was accomplished. Thereafter, a more flexible, adjusted dosage schedule was created by titrating injections of 5-fluorouracil according to the clinical appearance of the bleb. This served to minimize the effective dosage, which decreased the dose-related complications of 5-fluorouracil.

In all successful cases (nine patients), intraocular pressure was lower than 17 mm Hg. Despite the low dose of 5-fluorouracil (mean, 28 mg of 5-fluorouracil per eye compared to 105 mg[6] or 34.4 mg[12] per eye previously reported), the clinical response was at times dramatic. The good control of intraocular pressure was associated with elevated, more diffuse, and less vascularized blebs and an increase of microcystic changes indicating better filtration.[16] Not a single case of conjunctival wound leak was encountered, which suggests the real advantage of delaying therapy. The conjunctival incision heals properly, and bleb failures subsequent to conjunctival wound leaks are avoided.

Despite the low dose of 5-fluorouracil, corneal epithelial defects occurred in six patients. This complication, however, should be regarded as dose-related, because in all affected eyes, a total dose of more than 30 mg of 5-fluorouracil had been administered. We believe that the high continuous rate of corneal epithelial proliferation may explain this toxic effect even weeks after surgery. These corneal epithelial defects were rarely associated with a protracted course, and they, unlike conjunctival wound leaks, should not directly affect the outcome of filtration surgery.

The mean follow-up time in our patients was 13.7 months (range, ten to 17 months). We believe it is appropriate to report our data at this time because in a large national study that involved 155 eyes most failures occurred within eight months (78% in aphakic eyes and 86% in eyes with previously unsuccessful filtration surgery).[17] This suggested that our data reflect the intermediate outcome of this procedure. 5-Fluorouracil dosage, as recommended by Heuer, Parrish, and Gressel,[6] although effective, may be associated with a high complication rate. One of these complications, conjunctival wound leaks, may be responsible for some of the filtration failures. By modifying the administration of 5-fluorouracil as described, we can make the procedure more practical and perhaps more beneficial by avoiding the occurrence of conjunctival wound leaks while still maintaining an effective therapeutic dose at the filtration site. Additionally, with careful observation for clinical failure, the subconjunctival scarring process can be interrupted or reversed with the end result being successful filtration. This may allow the use of 5-fluorouracil only in those patients in whom failure during postoperative observation seems likely, rather than in all patients who conform to predetermined criteria for an increased likelihood for failure.

We understand that our study has the shortcomings of few patients and no concurrent control subjects. We hope, however, that our results stimulate the initiation of a larger prospective study to confirm the viability of the modified administration of 5-fluorouracil.

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OPHTHALMIC MINIATURE

At a solitary table there was a couple in hiking gear—knapsacks and sling bags and cameras. I was eating my breakfast thinking: Is this a mistake? One of the old men was staring at me. It made me very uneasy, the way he was gasping, but then I noticed that his glasses were very thick, and thought that perhaps he was not staring at me, but only looking out of his glasses, the way people look out of windows on rainy days.

Paul Theroux, *Riding the Iron Rooster*
New York, Ivy Books, 1988, p. 5

A Refractive and Histopathologic Study of Excimer Laser Keratectomy in Primates

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Using a 193-nm excimer laser, we produced wide-area, refractive keratectomies on 18 cynomolgus monkey corneas and followed them up for up to 18 months. All corneas developed some subepithelial haze by one month. Electron microscopy disclosed epithelial thickening, absence of Bowman's layer, and subepithelial activated fibroblasts surrounded by disorganized collagen. By six months, the haze faded to a variable degree, the epithelium regained normal thickness, and the collagen was more organized. Persistent corneal haze at 12 months in some corneas correlated with electronlucent spaces in the subepithelial zone. Corneas were 90 μm thinner centrally two weeks after myopic ablation, but returned to preoperative thickness by six months. Myopic flattening and hyperopic steepening of 6 diopters were targeted, and over 7 diopters of each were achieved initially. Regression of induced curvature stabilized over several months. At 18 months, 4.4 diopters of myopic flattening and 5.2 diopters of hyperopic steepening remained.

CORNEAL SURGERY using ultraviolet radiation from an excimer laser is being widely investigated.[1-11] The interaction of 193-nm laser energy with tissue results in uncoupling of molecular bonds or ultrafast thermal events that cause ejection of ablated tissue at supersonic velocities, or both.[2,12,13] Because these effects are limited to the surface of the area treated,[1] and energy is delivered in discrete pulses (commonly at ten pulses per second), the amount of tissue excised can potentially be controlled with limited or negligible effects on adjacent tissue.

When delivered through a linear slit, the excimer laser functions as a knife ablating a deep narrow channel. This technique has applications in refractive surgery, such as radial keratotomy and astigmatic surgery, and in corneal transplantation.[1,4,14] Delivered over a broad area, the energy can be used to resect corneal lamellae over a diameter ranging from 4 to 7 mm.[15] When delivered through changing apertures, the corneal curvature can be altered, correcting refractive errors of myopia, hyperopia, and astigmatism.[16]

As in other forms of corneal surgery, secondary biologic responses of the tissue will influence which excimer laser treatment modalities prove successful.[17,18] We treated 18 cynomolgus monkeys with wide-area 193-nm excimer laser surface ablation in an attempt to alter the curvature of the anterior refraction surface of the cornea. Myopic, hyperopic, and control keratectomies were performed, and the monkeys have been followed up for as long as 18 months to assess the clinical appearance and changes in refractive power of the corneas and the histopathologic appearance of tissue responses. This study was run concurrently with our previously reported human series[11] and provides an additional opportunity to study the optical and histopathologic changes that occur with corneal wound healing after excimer laser lamellar keratectomy over time.

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Material and Methods

A 193-nm argon fluoride laser with a beam-modifying optical system, which has been described previously,[19] was used in our experiments.

The total laser energy output, as it entered the optical system, was 200 mJ. The laser beam was passed through an aperture mask and expansion prisms to smooth the energy profile, and it was then rotated with a K-mirror device to equalize the effect of the slightly irregular beam on the corneal surface. The laser output was measured before and during the treatment with a beam-monitoring device. The fluence or energy density at the surface of the eye was 85 to 100 mJ/cm^2, the maximum ablation diameter was 5.2 mm, and the pulse rate was 10 Hz. Each pulse was estimated to ablate to a depth of 0.1 to 0.3 μm. Ablation time was 60 to 80 seconds. These optimum laser parameters had been determined previously through experiments using 75 enucleated human eyes.

The laser was equipped with aperture wheels through which the beam was directed. One wheel produced an ablation that could correct myopia by flattening the cornea, and the other could correct hyperopia by steepening the cornea. The myopic wheel had a series of apertures of decreasing diameter, whereas the hyperopic wheel had a series of annular apertures of decreasing radial width. A stepper motor was used to drive the wheel to cycle the different apertures under computer control. The laser delivered a series of pulses at each aperture setting according to the preoperative specifications entered into the computer, which resulted in the different ablation depths and curvatures etched onto the surface of the cornea.

The effects of myopic and hyperopic ablation were studied in a group of 18 cynomolgus monkeys (*Macaca fascicularis*). Primates were chosen because of the presence of Bowman's layer. Each monkey received an initial examination consisting of slit-lamp examination; keratometry; ophthalmoscopic examination; retinoscopy; pachymetry with an ultrasonic pachymeter; and tonometry with a Shiøtz tonometer.

Monkeys were divided into three treatment groups. The first group of six monkeys received a myopic or corneal flattening ablation designed to correct 6 diopters of myopia. The second group of six monkeys received a hyperopic or corneal steepening ablation. Five of the latter monkeys received 6-diopter corrections and one received a 2-diopter correction. The third or control group consisted of three monkeys that received a stream of hydrated air across their corneas during the ablation, two monkeys that received no topical medications before or after the ablation, and one monkey that underwent a sham ablation in which all operative steps were performed, but the laser was not activated. One eye of each monkey received treatment. Each eye chosen for treatment had a clear cornea at preoperative examination.

Before ablation, monkeys were anesthetized with ketamine hydrochloride (25 mg/kg of body weight) and acepromazine (2 mg/kg of body weight) intramuscularly. Monkeys also received atropine (0.02 mg/kg of body weight) intramuscularly. The eye was fixed with sutures at the corneoscleral limbus, which were anchored to an eyelid speculum. Epithelium was removed with a blade centrally, leaving 1 to 2 mm of intact epithelium peripherally. The cornea was then centrally ablated over a 5.2-mm diameter surface area with either a myopic or hyperopic ablation using the laser parameters described above. The eye was kept moist before the ablation with topical balanced salt solution in all groups except that which received no topical medications.

Preliminary studies with cadaver eyes demonstrated that vaporized debris generated during corneal ablation led to uneven ablations unless it was removed during treatment by an airflow. For the monkey studies, effluent was removed by a vacuum suction tube held within 2 cm of the cornea.

Each cornea was inspected and photographed immediately after ablation to assess the quality and position of the laser treatment. Gentamicin (3 mg/ml) drops were instilled immediately after ablation, except in the two monkeys receiving no topical medication. The monkeys awakened in their cages and showed minimal signs of discomfort. No analgesics were needed, and no further therapeutic medications were used.

Full postoperative examinations were performed at two weeks, one month, two months, three months, six months, ten months, and 12 months after laser treatment. Under general anesthesia, slit-lamp examination, keratometry, and photography were performed, and central corneal thickness was measured ultrasonically. Streak retinoscopy was also performed.

Intraocular pressure was measured with a Schiøtz tonometer.

Monkeys from both myopic and hyperopic ablation groups were killed at one month, six months, and one year. In the monkeys killed at one month, the remaining untreated eye of each monkey was ablated with a myopic ablation immediately before death, one with hydration and the other without. At ten to 12 months after ablation, a morphologic comparison was made between a cornea that was judged to be moderately hazy by slit-lamp examination and one with very little interface haze. Corneal tissue from the ablation site was fixed in glutaraldehyde and examined by light microscopy, transmission electron microscopy, and scanning electron microscopy.

Results

Immediately after laser treatment, the finely spaced, concentric ring patterns of ablation were visible. The ablated corneal surfaces were finely textured, slightly more textured than nonablated Bowman's layer (Fig. 1).

At two weeks after ablation, the epithelial defects were completely healed in all monkeys. Variable migration of pigment from the heavily pigmented limbal conjunctiva extended into the area of ablation. Penlight examination showed haze centrally in the laser-treated zone in all monkeys. On slit-lamp examination, a mild-to-moderate fibrillar haze was evident in the ablated zone at the epithelial-stromal interface (Fig. 2). This haze was more pronounced in the regions of deepest ablation (centrally for myopic corrections and peripherally for hyperopic corrections). The amount of haze was variable between monkeys, but it was present in all monkeys. There was no evidence of recurrent epithelial erosion or anterior segment inflammation.

At one month, there was some clearing of the pigment centrally. The fibrillar haze was unchanged in most monkeys.

At two to three months after ablation, variability in the degree of interface cloudiness was seen. The initially speckled haze was more confluent in some eyes, and other eyes had less haze overall than previously. The pigment continued to diminish.

At six months, all laser-treated eyes had some corneal interface opacity, the amount of which varied markedly between monkeys. Three eyes showed a mild-to-moderate progression of haze with increased confluency. Four eyes demonstrated slight-to-marked regression and clearing of corneal cloudiness. Six eyes did not change significantly compared to the change at the two-month examination.

At ten to 12 months, little or no pigment was detected in the corneas. The interface haze was

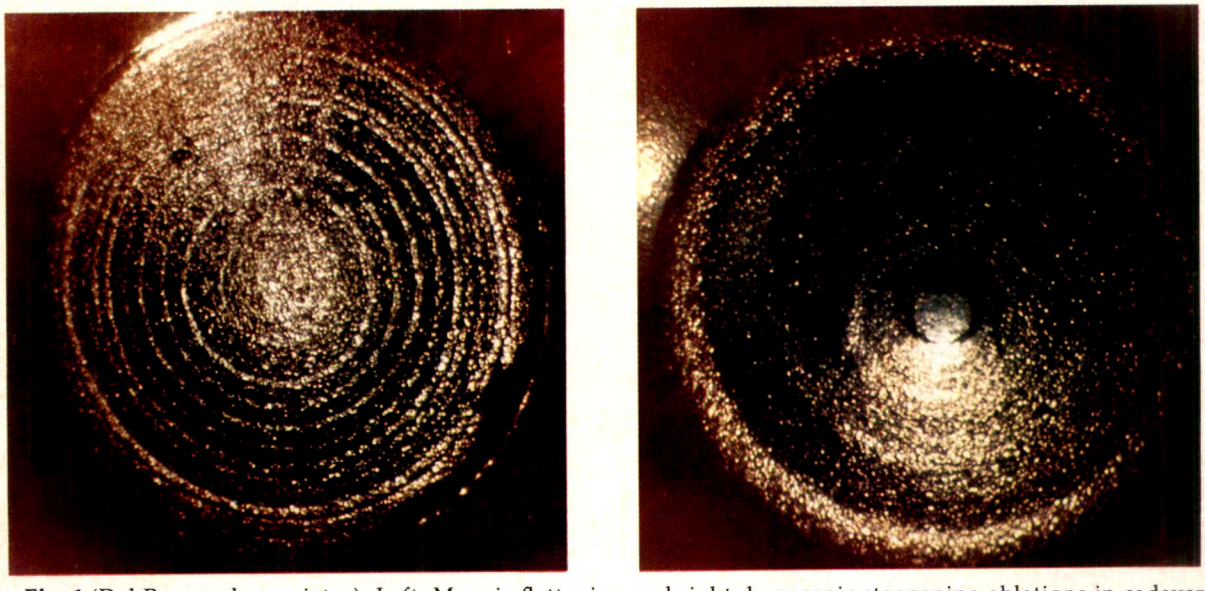

Fig. 1 (Del Pero and associates). Left, Myopic flattening and right, hyperopic steepening ablations in cadaver eyes immediately after surgery. The concentric ring patterns are visible as is the slightly textured surface of the ablations. The epithelium was removed centrally with a blade before the ablations.

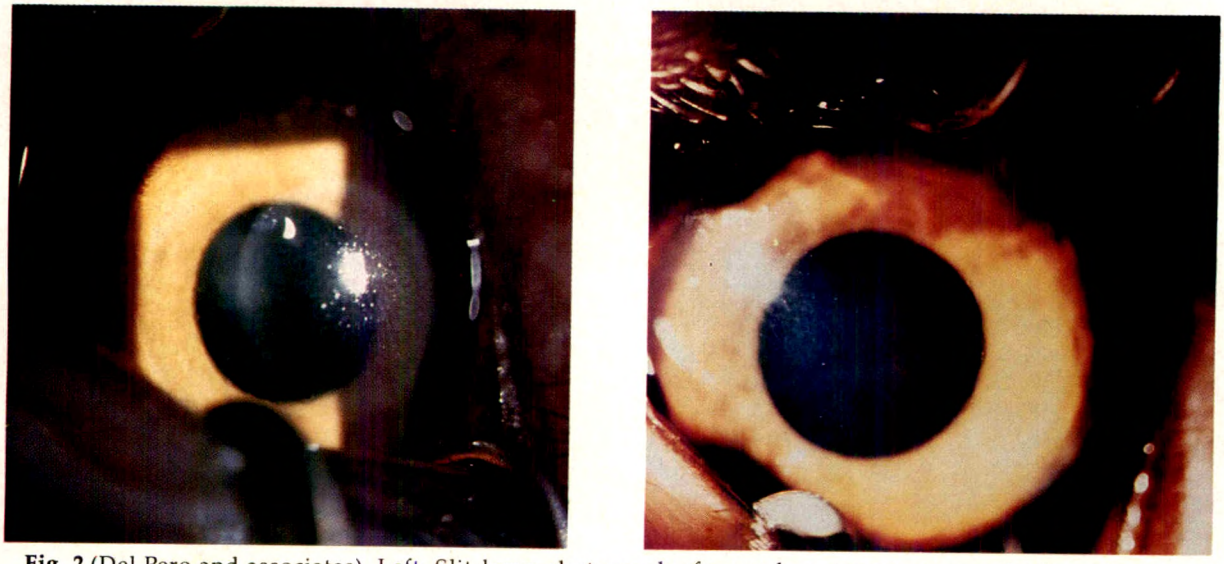

Fig. 2 (Del Pero and associates). Left, Slit-lamp photograph of a monkey cornea one month after a hyperopic ablation. The haze observed at the interface between the clear overlying epithelium and the underlying stroma is most noticeable peripherally where the ablation is deepest. This eye demonstrated a moderately severe degree of corneal clouding. Right, Slit-lamp photograph of a monkey cornea ten months after a myopic ablation. The interface haze was considerably less than at earlier examinations.

clearer than it had been at the six-month examination in many monkeys, with the zone of ablation difficult to detect by penlight examination. The slit lamp still disclosed some superficial opacification in all monkeys. Nine of the 12 remaining laser-treated monkey eyes (75%) had mild haze with regression overall, and three of the 12 eyes (25%) had moderate haze with slight progression and increased confluency. The control monkey eye that underwent a sham ablation remained clear.

The three monkey eyes ablated while their corneas were hydrated by humidified air were in the group showing initial progression of superficial corneal cloudiness with later regression to faint haze.

Retinoscopy appeared to be a better measure of curvature of the ablated cornea than standard keratometry. The ablated region was of a different dioptric power than the surrounding normal cornea and was evident by retinoscopy. Keratometry was difficult because of problems in accurately aligning the ablated cornea of the anesthetized monkey with the keratometer mires. The reflection of the keratometer mires, at 3.2-mm diameter, lay near the edge of the ablation zone, especially in the hyperopic group. The hyperopic ablation had a 5.2-mm outer diameter, but the optical zone was smaller because of the peripheral blending curve.

Central pachymetry in the myopic group provided a measure of ablation depth and of the subsequent healing response. Central pachymetry in the hyperopic group did not correlate with ablation depth because the central 1 mm of cornea was not ablated. Peripheral pachymetry in the deepest region of hyperopic ablation was not performed because of the variability in sequential measurements.

The quantitative data of corneal curvature and thickness for the myopic group are shown in Figure 3. After epithelial healing, the average central corneal ablation depth at two weeks was 90 μm. The corneas progressively thickened, and by six months they were within 10 μm of the preoperative values, a loss of almost 90% of the initial central ablation depth. Both keratometry and retinoscopy showed initial flattening of corneal curvature with partial loss of refractive effect in the first one to two months postoperatively with a tendency toward more stability with time. Initially, 7.4 diopters of average flattening was obtained as measured by retinoscopy. By one year, 4.4 diopters of net flattening (59% of initial refractive effect, or 73% of the intended 6.0 diopters of correction) was still present.

The results for the hyperopic group are shown in Figure 4. Retinoscopy showed an average steepening initially of 7.3 diopters. By one year, 5.2 diopters of steepening (71% of initial refractive effect, or 87% of the intended 6.0-diopter correction) was still present.

Results from the control groups of monkeys

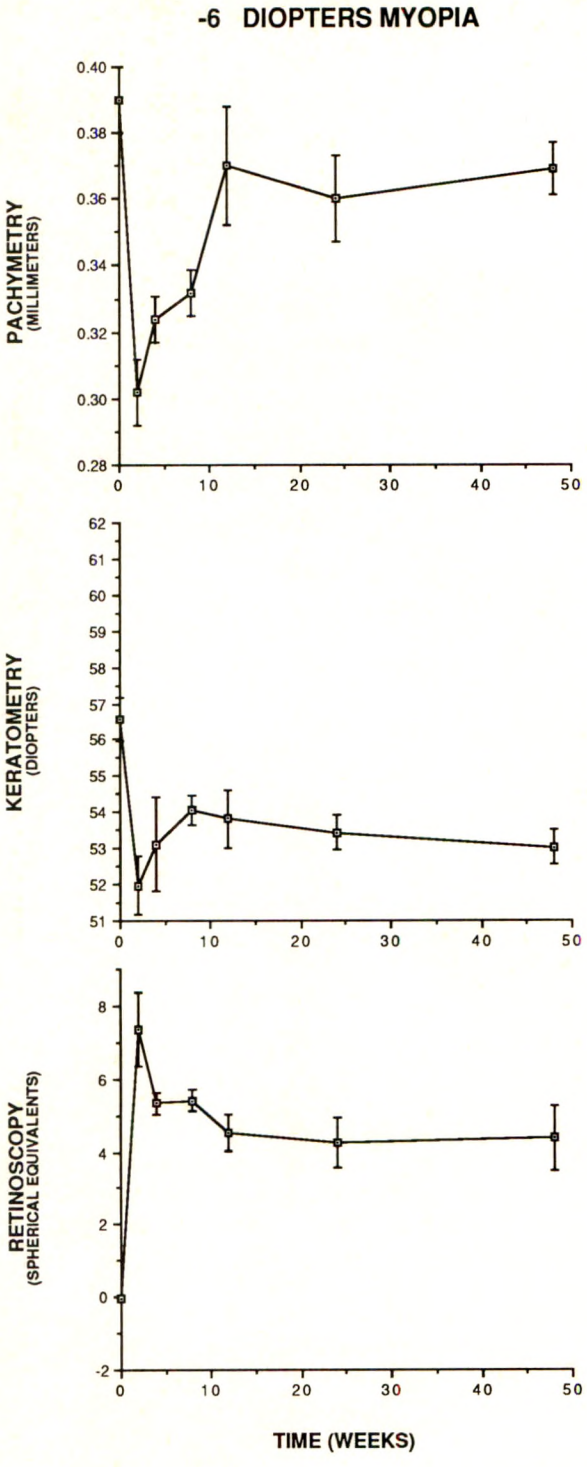

Fig. 3 (Del Pero and associates). Corneal thickness (measured by ultrasonic pachymetry) and curvature (measured by keratometry and retinoscopy) for the myopic monkey eyes over a one-year postoperative period are shown. The target value for central corneal flattening was 6.0 diopters. Vertical bars represent standard errors of the mean. This group contained six corneas initially, and four corneas after eight weeks because some animals were killed.

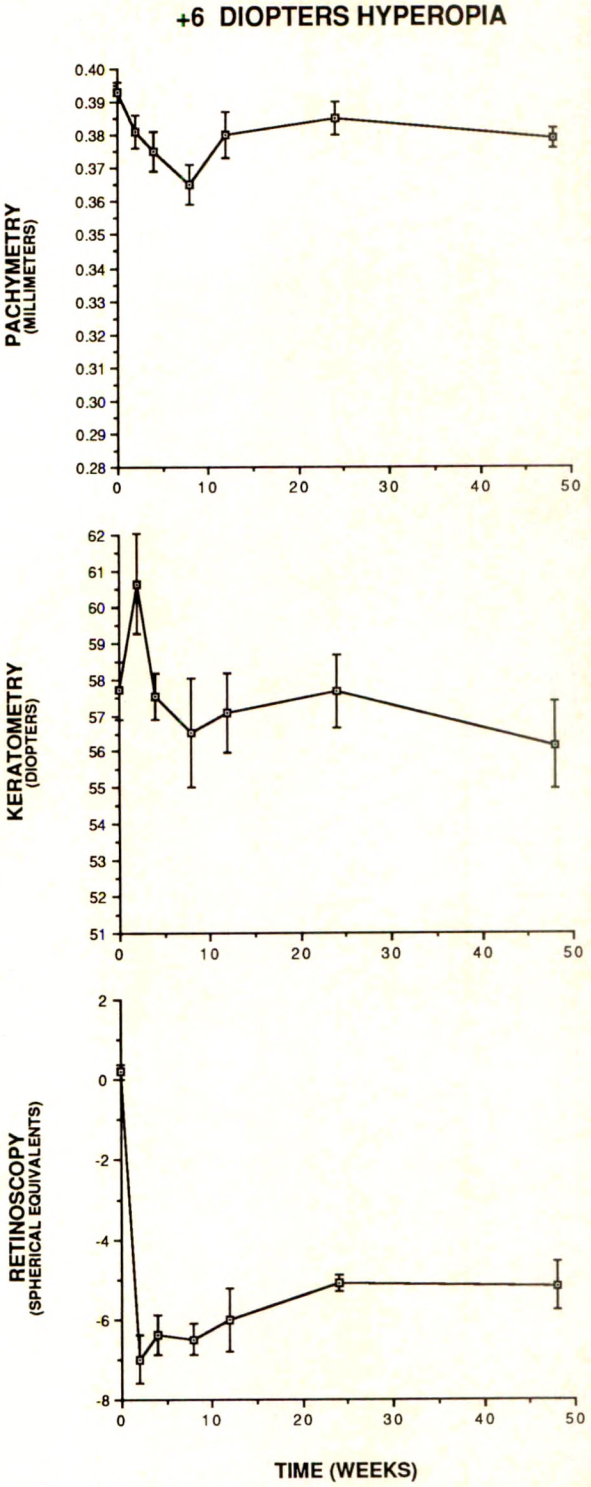

Fig. 4 (Del Pero and associates). Serial measurements of pachymetry, retinoscopy, and keratometry for the hyperopic monkeys followed up for almost one year after laser ablation are shown. The target value of central corneal steepening was 6.0 diopters. Pachymetry of the central cornea was of nonablated tissue and therefore was stable over time. Keratometry was problematic because of difficulties in positioning the keratometer mires accurately within the ablation zone. This group contained six corneas initially and four corneas two weeks after ablation.

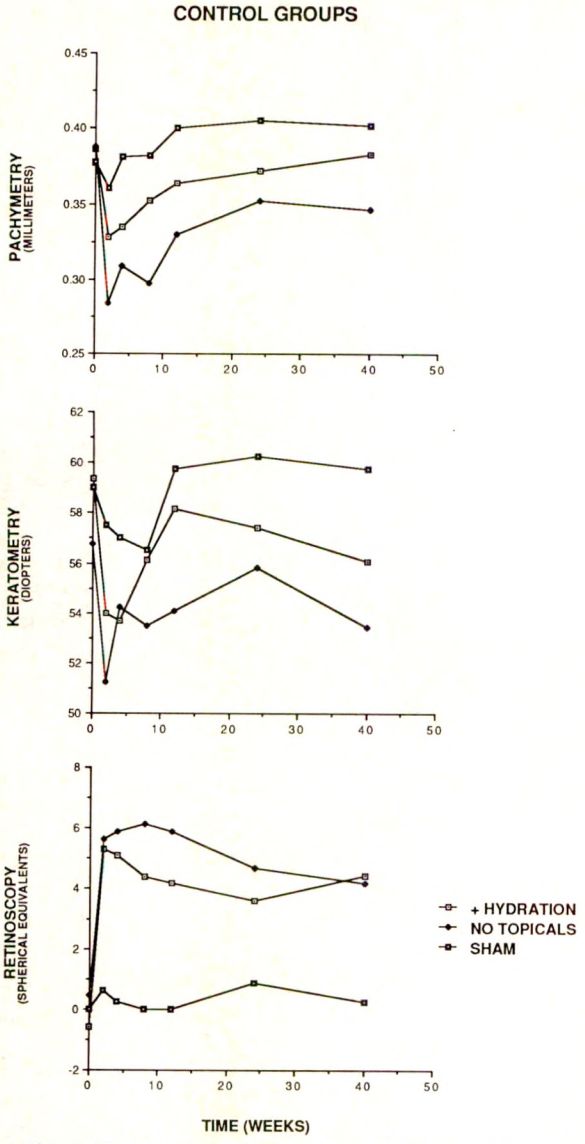

Fig. 5 (Del Pero and associates). Pachymetric and refractive data for the control groups are shown. The sham ablation group included corneas on which the standard procedure was carried out but without exposure to the laser. In this group, postoperative corneal thickness and curvature values did not vary significantly from preoperative values. In the hydration group, in addition to the standard procedure, three corneas were kept moist with humidified air throughout ablation. This group was reduced to two corneas at 40 weeks because some animals were killed. In the no topicals group, two corneas received no topical medications. The corneas in the hydration group and no topicals group received myopic ablations, and their corneal curvatures, as measured by retinoscopy, resembled those of the myopic group (Fig. 3).

are shown in Figure 5. The sham ablation did not significantly affect measurements of corneal thickness or curvature. The corneas in the remaining two control groups received myopic ablations and differed from the myopic group only in the perioperative treatment of the eyes. Two corneas received no topical medications, and three corneas were hydrated during the ablation. Examination of these remaining monkey eyes disclosed trends similar to the myopic group, which received the standard laser treatment. The monkey corneas receiving no topical medications lost about 65% of their initial central ablation depth by one year, and the corneas hydrated during ablation lost about 80% of the initial depth by ten months. The monkeys receiving no topical medication and those receiving hydrated ablations had over 5 diopters of initial flattening, of which 20% and 30%, respectively, was lost by six months, after which no significant further loss was observed.

Examination of corneal specimens immediately after myopic ablation disclosed an absence of epithelium, Bowman's zone, and the superficial stroma. The remaining stroma was unremarkable and contained collagen fibrils in a normal, orderly array even at the surface of the ablation (Fig. 6).

At one month after ablation, the epithelium over the ablated portion of the cornea was thicker than the epithelium over the nonablated cornea (Fig. 7). This was most pronounced in the deeply ablated periphery of the hyperopic specimen in which the epithelium was seven to nine cells thick, as compared to a normal nonablated control epithelium, which is four to five cells thick. At the same postablation period, the epithelium in the myopic specimen was five to seven cells thick. Hemidesmosomes were abundant in the basal epithelium, which was firmly adherent to the underlying stroma. The epithelium of the peripheral cornea contained intracellular melanosomes as did some fibroblasts in the superficial stroma. Beneath the epithelium, in the laser-ablated area, was a prominent zone of corneal fibroblasts (keratocytes) with a prominent, dilated, rough endoplasmic reticulum. The presence of the activated corneal fibroblasts implied active protein synthesis (Fig. 8). These fibroblasts, more numerous than usual, were surrounded by collagen fibrils and other components of the extracellular matrix. The collagen fibrils were less organized than in the normal corneal stroma. Several extracellular electronlucent regions were located in the

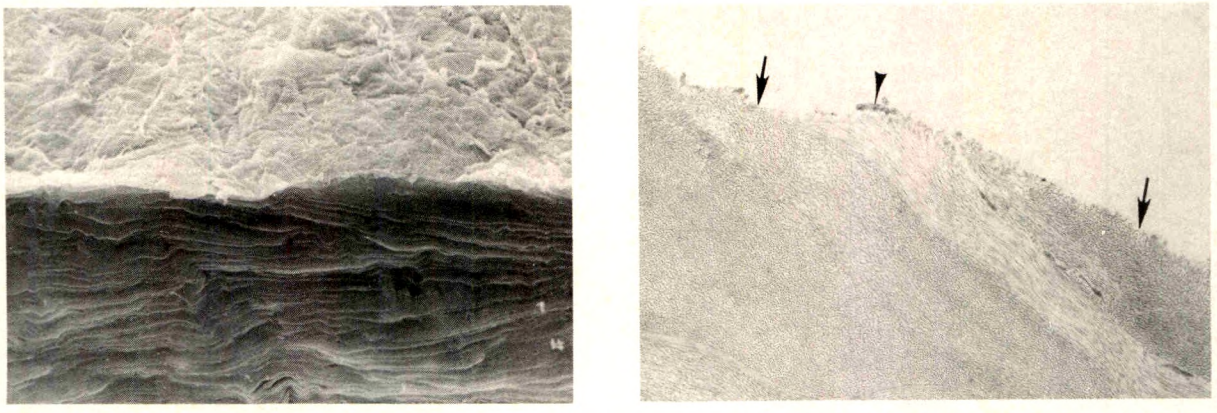

Fig. 6 (Del Pero and associates). A monkey cornea that was prepared immediately after a hyperopic ablation is shown. Left, Scanning electron micrograph shows the fibrillar texture of the ablated corneal surface. The lower half of the figure is a cross section through the stroma. Bowman's layer and the epithelium are absent (×650). Right, Transmission electron micrograph of the ablated portion of the cornea shows an absence of both the corneal epithelium and Bowman's layer. Few fragments of cellular debris (arrowhead) are adherent to the corneal stroma (arrows). The underlying collagen fibers appear normal (×5,900).

deeply ablated periphery of the hyperopic specimens.

At six weeks after ablation with the myopic wheel, one cornea, which appeared relatively clear by slit-lamp examination, had epithelium of normal thickness in the ablated area. The epithelium was adherent to a basal lamina and the underlying stroma, which contained fibroblasts that lacked a prominent dilated endoplasmic reticulum. These remaining fibroblasts had returned to a quiescent or more dormant state.

Six months after ablation, the epithelium overlying the ablated cornea was also of normal thickness and firmly adherent to a basal lamina, which was discontinuous at small focal sites, and to the underlying stroma. Subepithelial quiescent fibroblasts (Fig. 9) contained electron-dense particles.

At ten to 12 months, epithelium in the region of laser ablation was of normal thickness with no apparent ultrastructural abnormalities. The subepithelial stroma contained quiescent fibroblasts and collagen fibrils that were more closely spaced than those in the specimens from one month after ablation. At ten to 12 months after

Fig. 7 (Del Pero and associates). Transmission electron micrograph of the anterior stroma in the ablated region of a monkey cornea one month after a myopic ablation. Activated fibroblasts surrounded by disorganized collagen bundles and intercellular matrix are shown. Some corneal fibroblasts contain numerous melanosomes (arrow); others have only an occasional melanosome (arrowhead) (×5,400).

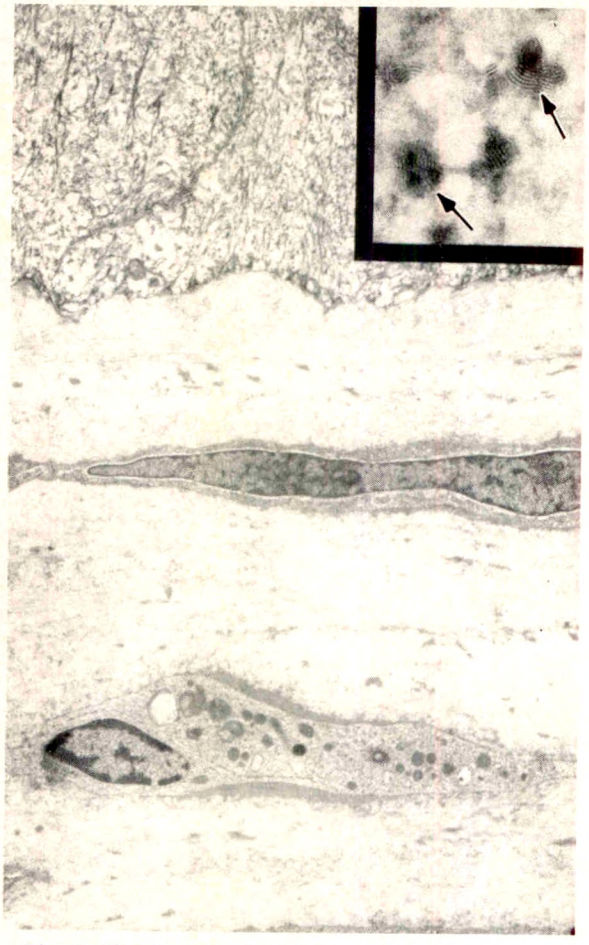

Fig. 8 (Del Pero and associates). Transmission electron micrograph from a monkey cornea five months after a myopic ablation. Relatively quiescent corneal fibroblasts lacking the dilated rough endoplasmic reticulum seen in Figure 7 are shown. Focal discontinuities are evident in the basal lamina between the corneal epithelium and stroma. Electron-dense granules can be seen in the subepithelial fibroblast (×6,800). The inset shows an extracellular, electron-dense, multilamellar profile, which may represent aberrant basal lamina material (×97,200).

ablation, prominent extracellular electronlucent areas were apparent between the collagen bundles in the zone of fibroblast activity in a specimen with moderate corneal haze but not in another specimen with minimal corneal haze (Fig. 9). The corneal epithelium, subepithelial fibroblasts, and rest of the cornea did not otherwise appear different in these two corneas.

No abnormalities were noted in the endothelium or deeper stroma in any of the laser-treated corneas. An inflammatory cell infiltrate and corneal neovascularization were absent in the specimens studied.

Discussion

The potential of excimer laser energy as a corneal surgical tool is great because of the many possible applications of precise keratectomy.[20,21] This pilot study involving primates sought to answer several questions: (1) Can the cornea heal with clarity after excision of Bowman's layer and the superficial stroma? (2) If healing involves a loss of corneal clarity, will opacities clear with time? (3) For applications in refractive surgery, can a new curvature be reproducibly created on the cornea, and, if so, what becomes of that new curvature with time? (4) What are the histologic correlates of the clinical and refractive observations as judged by light and electron microscopy?

In this study, all monkey eyes treated by laser keratectomy developed some opacification early in their postoperative courses. Early corneal clouding may have been caused by anterior stromal edema, perhaps reflecting incomplete epithelial maturity and cell-to-cell junctions. Another early cause of partial impairment of corneal clarity was melanin pigmentation, which implied migration of the pigmented conjunctival epithelium onto the cornea during resurfacing. This pigment essentially disappeared with time, presumably because it was progressively lost with epithelial turnover.

The most significant corneal opacification correlated with the presence of subepithelial activated fibroblasts and the presumed synthesis of new collagen and other components of the extracellular matrix. Such substances, initially laid down by these cells, are less organized than normal corneal stroma and scatter light more readily.

Although the clinically observed haze varied considerably between monkeys, the appearance of histologic specimens from monkey eyes was similar at any given postoperative time. In our study, the activity and number of fibroblasts decreased with time, and the subepithelial collagen became more organized with closer spacing of the collagen bundles. That these changes may have enhanced clarity is supported by the observation that extracellular electronlucent regions correlated with the persistence of cor-

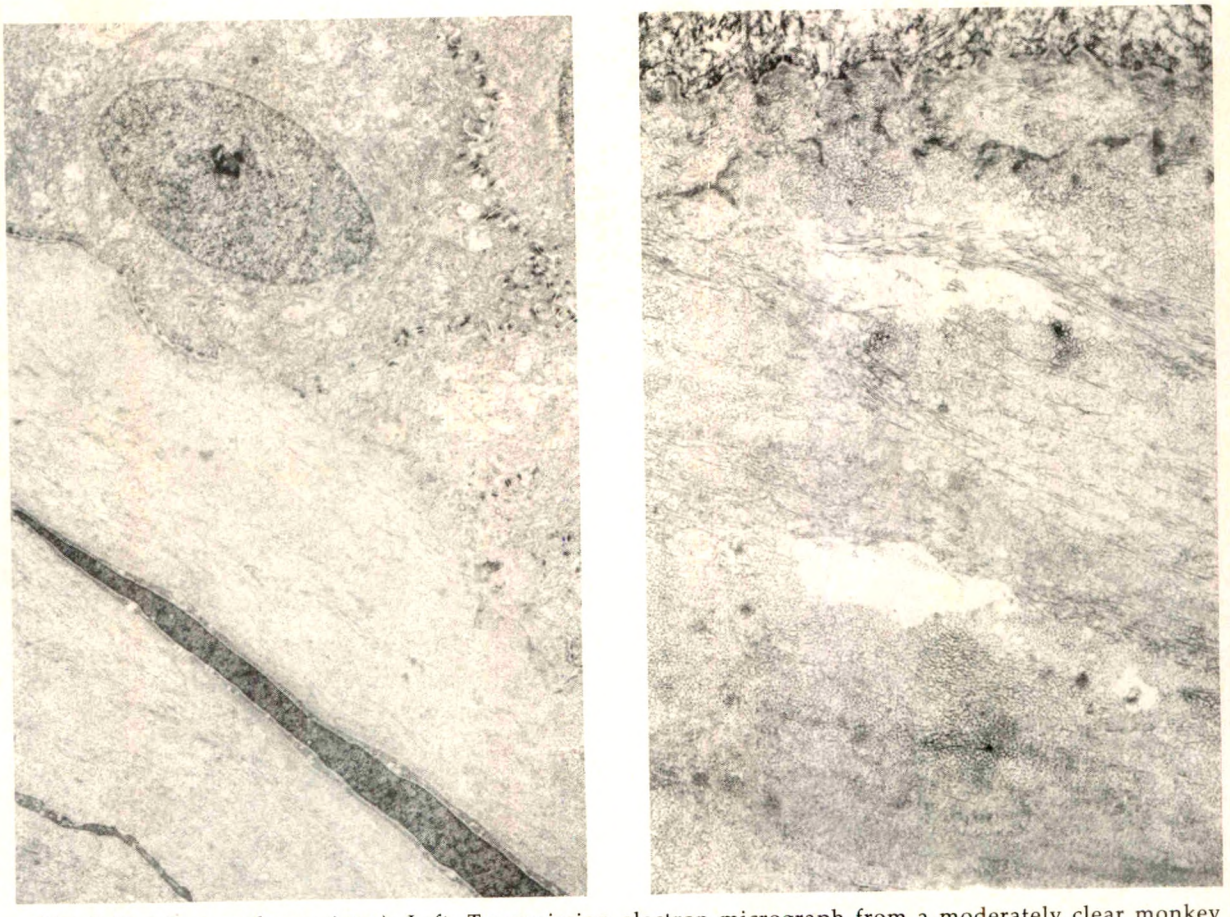

Fig. 9 (Del Pero and associates). Left, Transmission electron micrograph from a moderately clear monkey cornea 11 months after hyperopic ablation. Epithelial cells (above) are firmly attached to the basal lamina, which has focal discontinuities. Abundant hemidesmosomes are visible. Bowman's layer is absent. The stromal fibroblasts are quiescent, and extracellular electronlucent spaces are not seen between the collagen fibers (× 6,300). Right, Transmission electron micrograph from a moderately hazy monkey cornea 11 months after a myopic ablation. The epithelium (above) is normal and rests on stromal collagen. Bowman's layer is absent. The anterior stroma contains electronlucent spaces between the collagen bundles. In this specimen, corneal fibroblasts were quiescent and sparse and do not appear in this image (× 10,610).

neal haze in one of the specimens at one year after ablation, which suggests that extracellular accumulations may have caused the opacification by light scattering.

The refractive changes induced by laser keratectomy regressed over the first several months and then appeared to stabilize. With this study's limited sample size, the accuracy of the laser keratectomy can only be evaluated by trends; it cannot be evaluated by the statistical analyses possible in larger studies. Given limitations in technique, fairly reproducible curvatures correcting hyperopia and myopia were achieved by excimer laser keratectomy. In this study, which aimed at achieving 6 diopters of myopic or hyperopic ablation, the degree of final correction at one year was about 4 diopters for the myopic cuts and 5 diopters for the hyperopic cuts.

The mechanism of partial regression of the induced curvature remains to be defined. Possibly, the ablation zone fills with healing tissue, perhaps in a manner comparable to the eventual filling in of some corneal ulcers.[22] Pachymetry disclosed an initial increase in central corneal thickness in the myopic corneal ablations, which correlated with the histopathologic findings of an increased epithelial thickness

and a subepithelial fibroblastic response in the laser-ablated monkey eye. The relative contribution of the thickened epithelial and subepithelial tissue to the increase in corneal thickness was difficult to ascertain histologically, but corneal thickness appeared to stabilize as the fibroblastic response became less active with time. The increased number of corneal fibroblasts present in the ablated regions presumably reflected their migration from the adjacent cornea, or cell proliferation. In an immunohistochemical study of the monkey cornea after excimer laser ablation, Malley and associates[23] demonstrated the production of collagen types III and VI in the cornea after laser ablation. Type III collagen is not usually found in the normal mature primate cornea, and its presence is consistent with a healing response.

Although the central cornea after myopic cuts nearly returns to its preoperative thickness, the induced curvature only partially regresses. The epithelial facet and fibroblastic response extend over the entire ablation zone, with probable uniform thickening throughout the zone. This might explain the partial preservation of induced curvature observed with time. Other possible mechanisms whereby the cornea may partially regain its original curvature are anterior bulging caused by corneal thinning induced by the ablation, as seen in in situ keratomileusis,[24] or contractile forces exerted by subepithelial fibrous tissue on the cornea after laser keratectomy.

The magnitude of regression implies that a significant overcorrection will likely be necessary to achieve a desired final dioptric result. The magnitude of the overcorrection needed can be determined empirically, provided that the individual variation in the healing response is not too great. The reason for the variation in refractive results observed in this study remains unknown. Factors that may influence variability include difficulties in reproducibility of the ablations, as well as individual biologic differences. Additional masked studies with large samples, long-term follow-up, and further refinement of technique may help define the limitations that biologic variability exerts on excimer laser keratectomy.

Attempts to modulate the biologic response may focus on further characterizing the nature of the cellular reaction to ablation. The laser appears to remove tissue precisely without damage to underlying structures and without increase in unscheduled DNA repair.[25] Nevertheless, the possibility of cellular damage caused by direct ultraviolet irradiation or fluorescence and scattering from the area of ablation requires further study.

We tried to limit cellular damage caused by desiccation during ablation by delivering a water-saturated airflow to the corneal surface in three monkeys. This flow did not absorb the beam energy or limit the ablation (unpublished data). The corneas of these animals were among the clearest laser-ablated corneas throughout the follow-up period, but they still manifested an initial interface haze, which then decreased in severity.

To achieve several diopters of power change over a visually useful corneal diameter, it is necessary to ablate through Bowman's layer. The postoperative activity of the epithelium and keratocytes may be attributable to cellular communication between the cell types by means of diffusible substances[26,27] whose action is normally blocked, or which are otherwise modified by Bowman's zone. If this is true, it may be possible to prevent cellular interaction postoperatively with the use of pharmacologic agents, or perhaps by placing a barrier substance over the freshly ablated surface that could substitute for Bowman's zone.

Marshall and associates[28] reported a similar morphologic course in their long-term study of corneal healing after excimer laser keratectomy in a monkey model. In a companion human study,[11,29] some of us demonstrated similar clinical and morphologic findings after excimer refractive keratectomy. In that study, specimens available at three to 14 days and at four months after excimer laser treatment showed epithelial thickening and subepithelial activated fibroblasts apparently synthesizing new collagen and extracellular matrix. Overall, the corneal healing response of the monkeys was more pronounced and accelerated than that of the human patients, with greater interface haze, and perhaps a more rapid quiescence of fibroblastic activity.

The subepithelial fibrous reaction after excimer laser wide-area refractive keratectomy apparently accounts for the corneal haze that fades with time in most monkeys. Complete resolution of this cloudiness has not yet been observed. To be clinically acceptable, a high degree of corneal clarity after laser refractive keratoplasty involving the visual axis must be achieved. The underlying reaction to excimer ablation may be controlled by variations in

technique or by pharmacologic manipulation. Further studies in humans will be necessary to evaluate this technology adequately.

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Spontaneous Visual Recovery From Traumatic Optic Neuropathy After Blunt Head Injury

Mitchell J. Wolin, M.D., and Patrick J. M. Lavin, M.D.

Four patients who developed immediate blindness (no light perception) after indirect traumatic optic neuropathy caused by blunt head injury recovered vision without surgical intervention. In one patient, whose affected eye recovered to a visual acuity of 20/50 + 2, corticosteroids were not used. In two of the other patients, visual recovery began before corticosteroids were instituted. One patient recovered a visual acuity of R.E.: 20/15, one recovered a visual acuity of L.E.: 20/25 − 2, and one recovered a visual acuity of R.E.: 20/200 but with useful temporal field vision. Many investigators advocate aggressive surgical therapy for indirect neuropathy, particularly when corticosteroids fail. Significant recovery may occur despite no light perception, however, with medical therapy or even without therapy.

BLUNT HEAD TRAUMA, particularly to the forehead, may cause loss of vision as a result of optic nerve injury, even when the degree of trauma seems trivial.[1-5] The optic nerve is most vulnerable in, or at either end of, the bony optic canal, and at the muscle cone.[4] Direct injury may result from a fracture through the bony canal that severs or compresses the nerve, or bone fragments that lacerate the nerve.[2] The exact mechanism by which indirect injury to the nerve occurs remains uncertain. Shearing forces caused by abrupt deceleration of the skull may damage optic nerve fibers, but ischemia, caused by injury to small nutrient vessels, is the more likely mechanism.[1,2,4,6]

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Immediate loss of vision (no light perception) on impact indicates a severe optic nerve injury with a poor prognosis for recovery; a short period of vision (lucid interval) before deterioration suggests a potentially reversible process[7,8] and may warrant surgical intervention. The course of indirect optic nerve injury is unpredictable, making it difficult to define the roles of both corticosteroids in high doses and urgent optic nerve decompression.[2,6]

Our four patients sustained optic nerve blindness (no light perception) caused by blunt head injury, but all recovered useful vision.

Case Reports

Case 1

A 25-year-old man sustained a head injury in a motor vehicle accident. It was not clear whether he had lost consciousness; he was alert on arrival at the emergency room but could not remember details of the accident. He had a left zygomatic fracture under a large, raised skin and muscle flap. His visual acuity was R.E.: 20/25 and L.E.: no light perception. The right pupil was 3 mm, and the left pupil was 7 mm. The right pupil reacted briskly to light. The left pupil was amaurotic, with an intact consensual response. Ocular motility was normal. A small hyphema was present in the left eye. Intraocular pressures were R.E.: 25 mm Hg and L.E.: 33 mm Hg, by Schiøtz tonometry. Berlin's edema was observed superiorly in the left eye. Orbital computed tomography showed a soft tissue density consistent with hemorrhage behind the left globe (Fig. 1). Comminuted fractures were present at the apex of the orbit near the optic canal, but neither impingement of the optic nerve nor fracture through the canal were seen (Fig. 1).

Over the next six days, the patient's visual acuity remained L.E.: no light perception. Timolol maleate (0.5%) was administered for

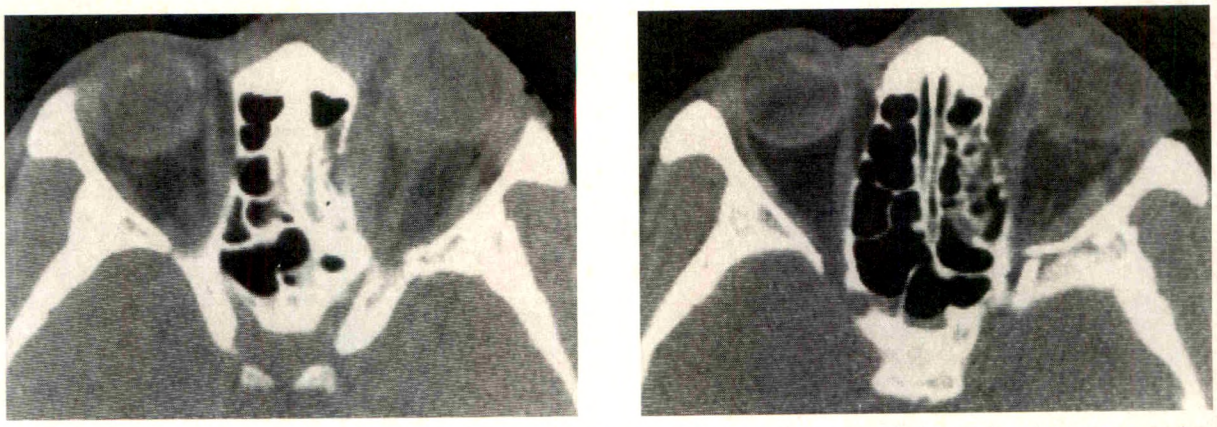

Fig. 1 (Wolin and Lavin). Patient 1. Left, Computed tomographic scan shows a soft tissue density just posterior to the left globe (Patient 1). Right, Comminuted fracture of the posterior cone of the orbit without optic nerve impingement, and multiple fractures of the medial orbital wall on the left with opacification of the ethmoid air cells are shown.

the first five days with normalization of ocular tension. No further hemorrhage occurred in the anterior chamber. Three weeks after the injury, the patient's visual acuity was R.E.: 20/30 and L.E.: 20/50, and the left pupil reacted partially to direct light. By six weeks, visual acuity in the left eye had improved to 20/40 − 2, although a relative afferent pupillary defect was still present. His left visual field showed mild, generalized constriction without segmental or focal deficits (Fig. 2). Five months later, the patient had left optic atrophy, but his visual acuity was R.E.: 20/30 + 3 and L.E.: 20/50 + 2 without correction.

Case 2

A 16-year-old boy was injured in a motor vehicle accident when he, restrained by a lap belt without a shoulder harness, struck his face on the windshield. He said he had not lost consciousness. In the emergency room, indirect ophthalmoscopy disclosed no light perception in both eyes. The patient's pupils were 4 mm in both eyes with a trace reaction to direct light in the right eye but none in the left eye. He had a partial-thickness right corneal laceration. Intraocular pressure was 30 mm Hg in the right eye and 15 mm Hg in the left eye by digital pneumotonometry. Ophthalmoscopy disclosed a peripapillary flame-shaped hemorrhage just temporal to the disk and mild Berlin's edema in the right eye. He had a 30% hyphema in the left eye; no lacerations were seen. Repeat examination three days later showed some mild vitreous hemorrhage in the left eye. Choroidal rupture was suspected superiorly. Orbital computed tomography showed distortion of the left globe. There were bone fragments in both orbital

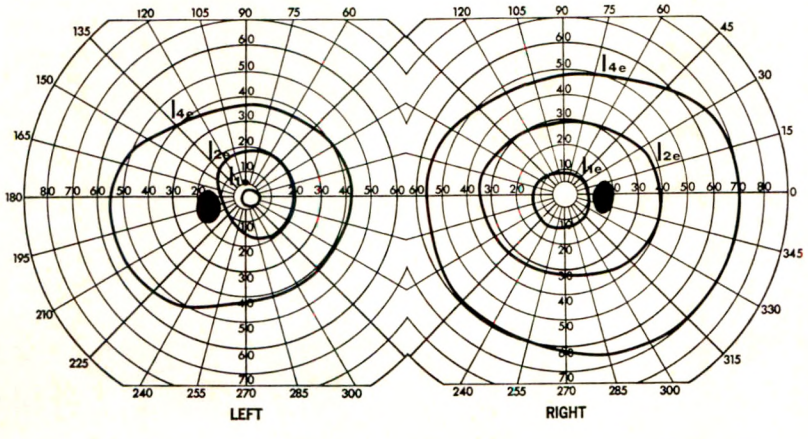

Fig. 2 (Wolin and Lavin). Patient 1. Goldmann visual field examination performed 11 weeks after injury shows mild constriction with reduction in central sensitivity of the field of left eye.

Fig. 3 (Wolin and Lavin). Patient 2. Computed tomographic scan shows multiple comminuted fractures of the nasal and ethmoid bones, the lateral wall of the left orbit, bone fragments in the soft tissues near the right globe, and fluid in the nasal sinuses.

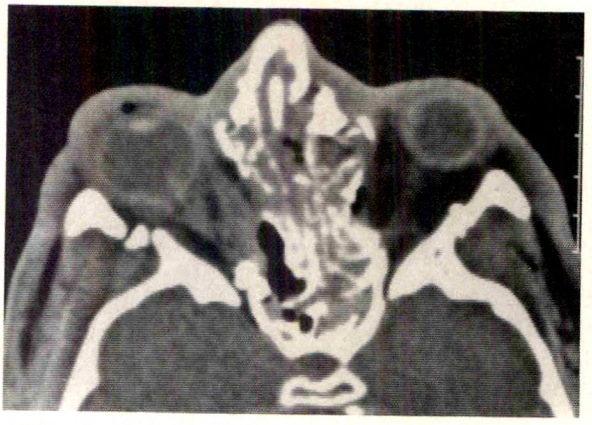

Fig. 4 (Wolin and Lavin). Patient 3. Computed tomographic scan shows multiple nasal and ethmoid fractures.

apices, but no definite nerve compression was identified (Fig. 3). The sclera appeared intact. Subsequent ultrasound disclosed no evidence of globe rupture or laceration.

Because the patient still had no light perception in either eye the day after injury, intravenous dexamethasone (10 mg every six hours) was administered. A few hours later, the patient's visual acuity was found to be R.E.: counting fingers and L.E.: hand motions. On the following day, his visual acuity was R.E.: 20/300 and L.E.: counting fingers, and five weeks later it was R.E.: 20/30 and L.E.: 20/200. The vitreous hemorrhage in the left eye cleared gradually. Later ophthalmoscopic examination confirmed areas of choroidal rupture superiorly in the left eye, without evidence of scleral rupture.

Six months later, the patient's visual acuity was R.E.: 20/25 and L.E.: 20/50 − 2. The left pupil was still unreactive. Because of a traction retinal detachment in the left eye, he had a vitrectomy membrane peel and cryotherapy. The patient's visual acuity 18 months after the accident was R.E.: 20/15 and L.E.: 20/25 + 2 with relatively normal confrontation visual fields, but mild left optic atrophy.

Case 3

A 17-year-old boy was injured in a motor vehicle accident when he, unrestrained by a seatbelt, struck his face on the dashboard. He did not lose consciousness. On arrival at the emergency room, he had no light perception in either eye, and his pupils were fixed and dilated. He had periorbital and nasal swelling with multiple facial lacerations. His fundi were not visualized. He was transferred to a secondary facility where on arrival his visual acuity was R.E.: no light perception and L.E.: light perception without projection. A computed tomographic scan showed fractures of the nose, orbital floors, walls of the ethmoid sinuses, cribriform plates, and periorbital rims. The right optic nerve appeared severed (Fig. 4). The following procedures were done: internal fixation of the nasal fractures, closed reduction of the nasal septum fracture, a left orbital floor implant with removal of a small piece of bone from the posterior orbit, and débridement and closure of the facial fractures. The optic nerve canal was not decompressed. After surgery, the patient continued to have a visual acuity of R.E.: no light perception and L.E.: bare light perception. Because of persistent light perception, he was transferred to a tertiary facility three days after the injury for consideration for optic canal decompression. On arrival, his visual acuity was R.E.: no light perception and L.E.: light perception. Both pupils were fixed and dilated, and he had complete bilateral ophthalmoplegia. His eyes were swollen shut with periorbital ecchymoses and lacerations as well as chemosis bilaterally. He also had a right subconjunctival hemorrhage. No blood was seen in either anterior chamber. An adequate view of the right fundus was not obtained because of the periorbital swelling. Examination of the left fundus disclosed choroidal rupture inferior to the optic disk. Intravenous dexamethasone, 10 mg initially and 4 mg every six hours thereafter, was administered. Later that

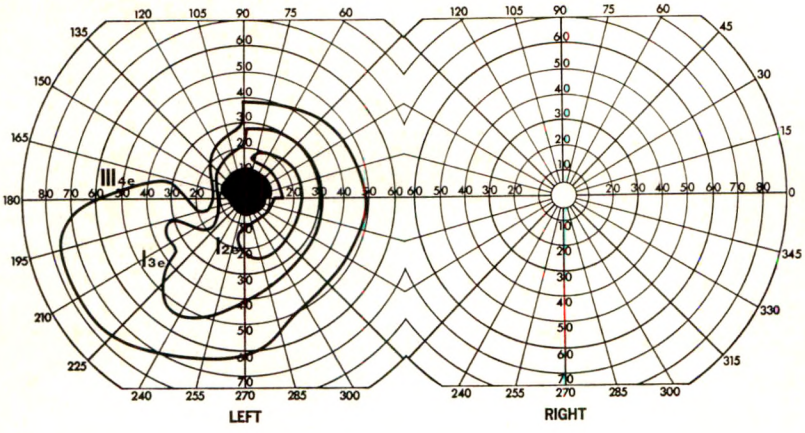

Fig. 5 (Wolin and Lavin). Patient 3. Goldmann visual field examination performed ten weeks after surgery shows a blind right eye and partial recovery of the field of the left eye.

evening, the patient's visual acuity was R.E.: no light perception and L.E.: counting fingers at three feet. On the fourth day after initiation of corticosteroids, his visual acuity was R.E.: no light perception and L.E.: 20/400. He was discharged on the sixth day on a regimen of tapering dexamethasone; his visual acuity was R.E.: no light perception and L.E.: 20/400.

Ten weeks later, the patient's visual acuity was R.E.: no light perception and L.E.: 20/25 − 2 without correction. He had a right relative afferent pupillary defect. His left visual field showed a large superior temporal defect with a relative central scotoma (Fig. 5). He could read only two of 24 Ishihara color plates and scored 60 points on Sahlgren's saturation test (normal, < 15). Ophthalmoscopy showed a glial scar obscuring the view of the right optic disk; the left disk was partially atrophic.

Case 4

A 23-year-old man, unrestrained by a seatbelt, was asleep in the passenger seat of a truck when it ran off the road and overturned. He was thrown from the truck and sustained a blunt head injury with a brief loss of consciousness. In the emergency room, he was alert and oriented and complained that he was unable to perceive light with his right eye at the scene of the accident and on arriving at the emergency room. Within 30 minutes of his arrival at the emergency room, an ophthalmologist found his visual acuity to be R.E.: counting fingers at two feet and L.E.: 20/20. His right pupil was dilated; he had both a right afferent and efferent pupillary defect. He had ecchymosis of the right upper eyelid with periorbital swelling. Results of direct and indirect ophthalmoscopy were normal. He had complete loss of abduction and some impairment of elevation and depression of the right eye; the left eye was normal. He had depression of the malar emminence on the right. Tactile ocular tensions were normal. He also had a puncture wound in the mid forehead associated with fractures of the anterior and posterior tables of the frontal sinus and laceration of the dura mater.

A computed tomographic scan of the head showed free air in the anterior cranial fossa on the right, fractures through the anterior walls of the maxillary sinuses with air in the orbit, air fluid levels in the ethmoid and maxillary sinuses on the right, and a fracture through the right optic foramen. There was no evidence of bony impingement of the right optic nerve (with coronal views), but the superior orbital fissure appeared distorted.

The following day, a regimen of 8 mg of intravenous dexamethasone was instituted every eight hours. Nine days later, the patient underwent an obliteration and cranialization procedure, with an osteoplastic frontal sinus flap.

Six weeks later, the patient's visual acuity, without correction, was R.E.: 2/200 and L.E.: 20/20. Color vision was impaired in the right eye (he could read none of the Ishihara color plates), but was normal in the left eye. Formal visual fields on a Goldmann perimeter showed a large central scotoma with a peripheral rim of preserved vision temporally and inferiorly (Fig. 6). He had a relative afferent pupillary defect and marked optic atrophy in the right eye.

Discussion

In these four patients, indirect injury to the optic nerve was the predominant cause of visu-

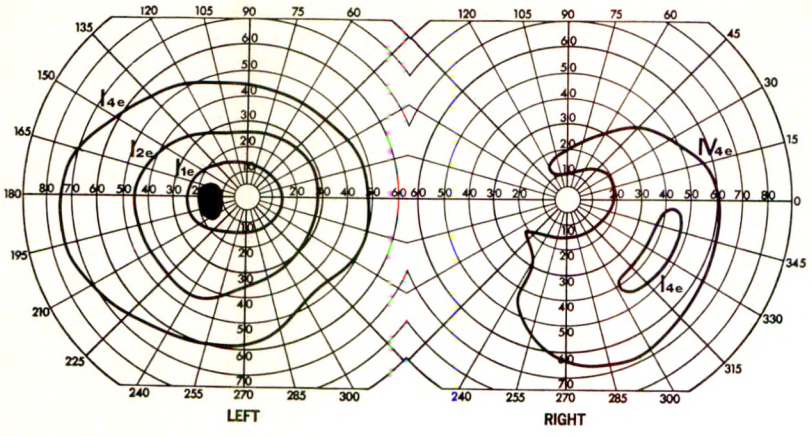

Fig. 6 (Wolin and Lavin). Patient 4. Goldmann visual field examination performed six weeks after surgery shows partial recovery of the field of the right eye.

al loss. The first patient had no light perception in the left eye with an amaurotic dilated pupil that reacted consensually. The degree of hyphema and retinal edema did not account for the severity of visual loss. The second patient had no light perception in either eye, and his intraocular injuries were not sufficient to account for complete loss of vision. The third patient had no light perception in either eye when examined in the emergency room, but a few hours later, he had bare light perception in the left eye. Vision in the left eye began to recover before corticosteroids were introduced, and the further improvement might have been spontaneous. The surgical procedure involved reduction of nasal fractures, repair of the left orbital floor, and removal of an orbital bone spicule remote from the orbital apex; the optic nerve was not decompressed. The fourth patient also had some improvement in vision before the administration of corticosteroids. These patients are remarkable for the extent of recovery after the condition of no light perception. The first patient is also remarkable for the long interval between the head injury and recovery of vision, particularly in the absence of corticosteroid therapy. The optic nerve dysfunction in our patients may have been caused by transient failure of conduction (neuropraxia), edema, or transient ischemia of the optic nerve.

In 1982, Anderson, Panje, and Gross[2] advocated the use of high-dose corticosteroids in traumatic optic neuropathy based on their experience with seven patients. Two patients recovered significant vision coincident with the use of corticosteroids, and two patients had a lesser degree of recovery, one after decompression of a subperiosteal orbital hematoma. Since then, there have been reports of similar successes,[3,9-11] although Tang and associates,[12] in a series of 37 patients, found corticosteroids unsuccessful. Several recent studies have reported the lack of efficacy, indeed sometimes harmful effects, of corticosteroids in other neurologic disorders, including cerebral trauma,[13] ischemic stroke,[14] intracerebral hemorrhage,[15] spinal cord injury,[16,17] and acute polyneuropathy.[18]

The first patient recovered useful vision (from no light perception) with neither corticosteroids nor surgical intervention. The third and fourth patients began to recover vision before the initiation of corticosteroids. The second patient had some improvement soon after the introduction of corticosteroids, but had a prolonged interval between the injury and significant recovery of vision. Our patients received neither megadose corticosteroids nor hyperosmolar agents. A spontaneous recovery is frequently attributed to the introduction of therapy. Only a controlled randomized trial, or observations of definite deterioration on withdrawal of medication with subsequent recovery on re-introduction in a number of patients, will clarify the efficacy of corticosteroids. Such a controlled randomized trial, however, is probably not feasible.[19]

A number of reports[2,6,9,20,21] of successful decompression of traumatic optic neuropathy after optic nerve injury support the role of surgery, even when it is delayed as long as five days[11]; Spoor and Mathog describe such a patient who had a penetrating knife wound.[11] Had our patients undergone decompressive surgery, the results would have been considered successful. When a compressive hematoma is present, the role of surgery seems clear; however, in the absence of such a hematoma, even with depressed bone fragments, the indications for surgery are less obvious. Whether a craniotomy with decompression of the optic nerve canal and falciform ligament is superior to the transethmoidal approach is also controversial.[20] Re-

ports of optic nerve decompression are difficult to evaluate because they are uncontrolled and not randomized.[2,6,8,9,20-24] In the series of Fukado[22] and Niho, Niho, and Niho,[23] the operative results were excellent; these studies, however, are criticized[2,9] for poor documentation and patient selection. Investigators, however, have found little benefit in optic nerve decompression in patients who have had immediate blindness caused by injury.[2,12,24] Although a controlled randomized trial is probably not feasible, a central data bank for the accumulation and analysis of information on patients with indirect optic nerve injury may help clarify the management of this condition.[19]

The results of this study illustrate the potential for spontaneous recovery in patients with immediate blindness after injury and contradict the idea that an amaurotic pupil indicates irreversible visual loss.[25] We believe that the only clear indication for surgical intervention in indirect optic nerve trauma, in the absence of a compressive lesion, is where visual loss initially improves with corticosteroid therapy and then repeatedly deteriorates with tapered doses.

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Analysis of 135 Autopsy Eyes for Ocular Involvement in Leukemia

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To explain the marked variation in the reported incidence of how often leukemic cells infiltrate the eye in fatal cases of leukemia, we tested the hypothesis that ocular leukemic infiltration is related to the peripheral leukocyte count during the final hours of life. We reviewed tissue sections, as well as autopsy and clinical records, from 135 patients who had fatal leukemia and had their eyes examined after death at Duke University Medical Center. Infiltrates of leukemic cells were found in the eyes of 42 of 135 patients (31.1%), with the choroid being the most frequently involved site. We detected a significant positive correlation between the ocular leukemic infiltration and an agonal leukocyte count as well as the severity of systemic disease. Differences in the agonal circulating leukocyte count may partly explain variations in the incidence of leukemic infiltrates in different postmortem studies.

OCULAR INVOLVEMENT in leukemia, first described by Liebreich in 1861,[1] may be an initial feature of the disease[2-4] or the first manifestation of relapse after remission-inducing chemotherapy.[5,6] In fatal cases of leukemia, leukemic cells commonly infiltrate the ocular tissues, although this is not apparent in every case. Based on the frequency of ocular leukemic cell infiltrations in fatal cases of leukemia and the known incidence of this disease in the United States,[7] one can estimate that between 5,100 and 14,480 patients with leukemia die in the United States annually with ocular manifestations.[8,9] This estimate lacks specificity because the incidence of ocular leukemic involvement (28% to 80%) varies in different postmortem studies. In some studies, no distinction is made between the leukemic cell infiltration of the eye and secondary ocular changes, such as hemorrhage, neovascularization, and infections. We undertook this study to determine the relationship between the frequency of ocular leukemic cell infiltrations and the circulating leukocyte count during the final hours of life.

Material and Methods

The present study is an extension of one performed by Nelson, Hertzberg, and Klintworth.[8] Tissue sections of the eyes, as well as other autopsy and clinical data, were reviewed on 135 leukemic autopsy patients at Duke University Medical Center between 1973 and 1987. At least one eye in each case had been examined after death by both gross inspection and light microscopy. Each eye was sectioned horizontally, and the central third was processed by standard methods. To increase the surface area for histologic evaluation, the retina and choroid were dissected from the sclera of the superior and inferior calottes in 87 eyes. These specimens were dehydrated through graded alcohols and rolled up before being embedded in Paraplast as retinochoroidal scrolls. Histologic sections were stained with hematoxylin and eosin and with other stains when appropriate.

The autopsy and clinical records were reviewed to determine the type of leukemia, therapy, number of clinical remissions, clinically recorded eye lesions, the cause of death, the presence or absence of a terminal remission,

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and other potentially relevant factors. In most patients, the agonal values of the total and differential leukocyte counts, platelet count, and hematocrit level were obtained within the 24 hours preceding death. Cases in which these hematologic values were not available during the 48 hours before death were excluded from analyses involving peripheral leukocyte counts and ocular leukemic cell infiltrations.

In 85 of 135 cases, bone marrow specimens and peripheral blood smears were reviewed to classify the cases of acute leukemia according to the French-American-British classification.[10] In the remaining 50 patients, pretreatment bone marrow smears were not available for review and were not classified under the French-American-British system.

The extent of terminal systemic leukemia was determined by evaluating the presence of leukemic cell infiltrates in the bone marrow, lymph nodes, spleen, liver, lung, heart, pancreas, kidneys, brain, and meninges.

The relation between ocular leukemic cell infiltration and systemic disease or the agonal circulating leukocyte count was analyzed in the 114 patients in whom appropriate data were available (Fig. 1). The more commonly used parametric statistical procedures such as analysis of variance were not appropriate because they require that observations be selected from normally distributed populations with equal variance. These data were more appropriately analyzed by nonparametric procedures, which impose no restrictions on the distribution of the populations. Accordingly, probabilities were determined by computing the Goodman-Kruskal index (γ),[11] which depends only on the relative rank of points within a distribution. (The Goodman-Kruskal index is as follows: $\gamma = [C - D]/C + D$, where C represents the number of concordant pairs of observations and D is the number of discordant pairs. A pair of observations $[(X,Y), (X',Y')]$ is concordant if $X > X'$ and $Y > Y'$ or $X < X'$ and $Y < Y'$, discordant if $X > X'$ and $Y < Y'$ or $X < X'$ and $Y > Y'$, and tied otherwise. This index is distributed as a random, normal variable even if the observations are not, hence a Z-score and probability value can be determined.[11]) Calculation of these values was done by a matched-pair partial correlation procedure.

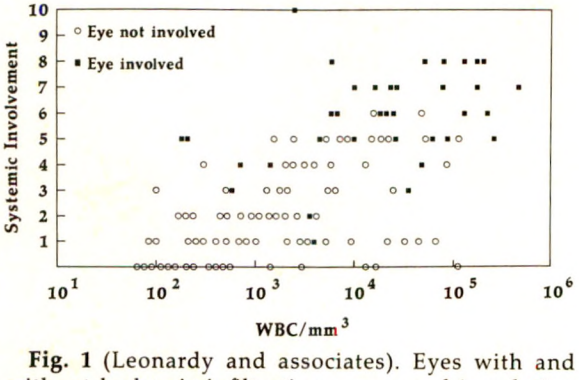

Fig. 1 (Leonardy and associates). Eyes with and without leukemic infiltrations expressed in relation to both the terminal leukocyte count in the peripheral blood and the extent of systemic disease (reflected by the number of organs with leukemic infiltrations). Note that eyes with leukemic infiltrates tend to be associated with more organ involvement and higher leukocyte counts than eyes without leukemic infiltrates.

Results

The overall incidence of ocular leukemic cell infiltrations in the 135 patients with leukemia was 31.1% (42 of 135 patients). In addition to these patients who had obvious leukemic infiltrates in the eye, occasional leukemic cells were observed in the stroma of the posterior choroid in 12 other patients. In eight more eyes, leukemic cells were noted inside the choroidal vessels but not extravascularly. If eyes with intravascular and occasional extravascular leukemic cells were considered positive, the incidence of ocular leukemic cell infiltrations was 45.9% (62 of 135 patients). The frequency of ocular leukemic cell infiltrations tended to gradually decline over time during the period of the study (Fig. 2).

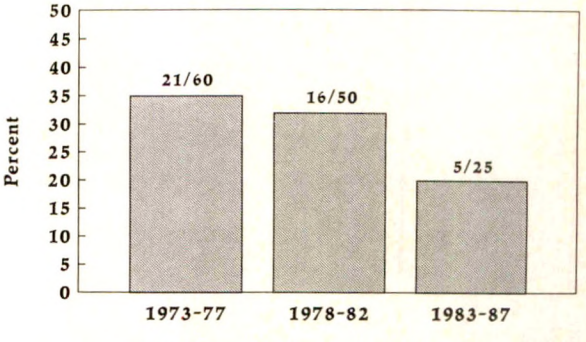

Fig. 2 (Leonardy and associates). The frequency of ocular leukemic infiltrations during different time periods between 1973 and 1987.

Of the seven patients who had no documented chemotherapy, five had leukemic infiltrates of the ocular tissues.

Although the incidence of ocular leukemic cell infiltrations in the acute leukemias was slightly higher (32.3% [32 of 99 patients]) than that of the chronic leukemias (27.8% [ten of 36 patients]) (Table 1), this difference was not statistically significant. Acute granulocytic leukemia (French-American-British Cooperative Group classification type M2 [acute myeloblastic leukemia without maturation]) and acute myelomonocytic leukemia (French-American-British Cooperative Group classification type M4 [acute myelomonocytic leukemia]) involved the ocular tissues more frequently than the other French-American-British Cooperative Group subgroups of leukemia (Table 1).

Leukemic cell infiltration of the eye correlated positively with an increased agonal leukocyte count in the peripheral blood (Fig. 1). By the matched-pair correlation procedure, this relationship was highly significant ($P < .0001$). The mean white blood cell count of patients with ocular leukemic cell infiltrates was $65,227/mm^2$; it was $10,500/mm^2$ in individuals in whom the eyes were not involved in this way (Fig. 3, left). Ocular infiltrates with leukemic cells correlated positively with advanced systemic disease as defined by the number of organs involved ($P < .0001$) (Fig. 1). The number of organs affected by leukemia also correlated positively with agonal leukocyte counts in the blood ($P < .0001$) (Fig. 1). More organs were affected by leukemia in patients with ocular leukemic cell infiltrates than in those without ocular involvement (Fig. 3, right).

When leukemic cells infiltrated the eye, they also infiltrated the brain in ten of 41 patients (24.4%). The brain was not examined in the other patient with ocular leukemia. Conversely, leukemia of the central nervous system was associated with leukemic cell infiltrates of the eye in ten of 13 (76.9%) cases.

Ocular hemorrhage was observed in 35 of 135 patients (25.9%). In 19 of these patients, plate-

TABLE 1
INCIDENCE OF OCULAR INVOLVEMENT IN DIFFERENT TYPES OF LEUKEMIA

TYPE OF LEUKEMIA*	NO. OF PATIENTS	PATIENTS WITH OCULAR INFILTRATIONS† (%)
Acute myeloblastic leukemia		
Acute myeloblastic leukemia without maturation (M1)	7	2 (28.6)
Acute myeloblastic leukemia with maturation (M2)	18	9 (50)
Hypergranular promyelocytic leukemia (M3)	1	0 (0)
Acute myelomonocytic leukemia (M4)	16	8 (50)
Pure monocytic leukemia (M5)	0	—
Erythroleukemic leukemia (M6)	3	0 (0)
Megakaryocytic leukemia (M7)	0	—
Unclassified acute myeloblastic leukemia‡	37	8 (21.6)
Acute lymphoblastic leukemias		
Homogenous acute lymphoblastic leukemia (L1)	1	0 (0)
Heterogenous acute lymphoblastic leukemia (L2)	3	1 (33)
Acute lymphoblastic leukemia with characteristics of Burkitt's lymphoma (L3)	0	—
Unclassified acute lymphoblastic leukemia‡	13	4 (30.8)
Hairy cell leukemia	1	1 (100)
Chronic myelocytic leukemia	23	4 (17.4)
Chronic lymphocytic leukemia	12	5 (41.7)
Total acute leukemia	99	32 (32.3)
Total chronic leukemia	36	10 (27.8)
Total all leukemias	135	42 (31.1)

*French-American-British Cooperative Group classification given in parentheses.[29]

†Includes only patients with obvious extravascular leukemic infiltrates.

‡Includes patients in whom pretreatment bone marrow smears were not reevaluated during this study for French-American-British Cooperative Group classification.

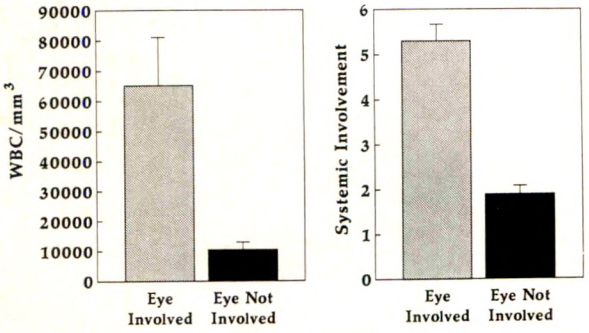

Fig. 3 (Leonardy and associates). Left, Mean white cell count in patients with and without ocular leukemic infiltrates. Right, Systemic involvement as reflected by the mean number of organs involved in patients with and without ocular involvement. The bars indicate the standard errors of the mean.

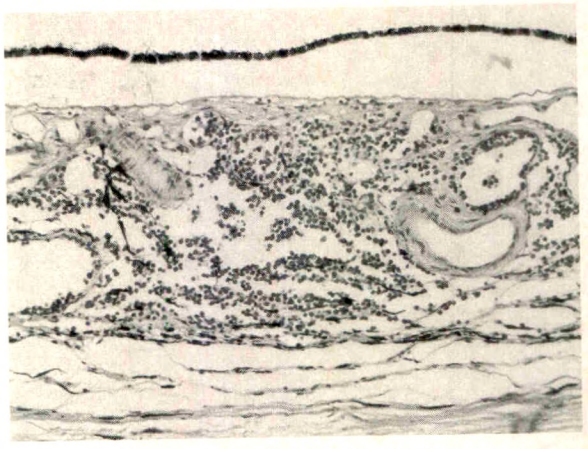

Fig. 4 (Leonardy and associates). Extravascular, acute, lymphoblastic leukemic infiltration in the posterior choroid (hematoxylin and eosin, × 170).

let counts were obtained in the peripheral blood during the final hours of life. The mean agonal platelet count in individuals with intraocular hemorrhage was 30,605/mm^2; it was 58,176/mm^2 in patients who had no intraocular hemorrhage. This difference, however, was not significant using the paired student *t*-test or the matched-pair partial correlation procedures. Moreover, 21 leukemic patients with platelet counts in the circulating blood of less than 10,000/mm^2 before death did not manifest intraocular hemorrhage.

Leukemia was noted in the routine histologic sections in all but one of the affected eyes; in one patient, the leukemic cell infiltrates were noted only in the retinochoroidal scroll. Of the 42 patients with ocular leukemic cell infiltrates, 39 had choroidal involvement (Fig. 4). In all of these patients, except one, the posterior choroid was affected; the exception had a leukemic focus only in the peripheral choroid. Margination of leukemic cells in choroidal vessels was pronounced in two patients, both of whom had acute myeloblastic leukemia (French-American-British Cooperative Group classification type M2 [acute myeloblastic leukemia with maturation]) (Fig. 5). Twelve patients had perivascular leukemic cell infiltrates in the anterior episclera (Fig. 6); all of them also had posterior choroidal involvement. Seven eyes had infil-

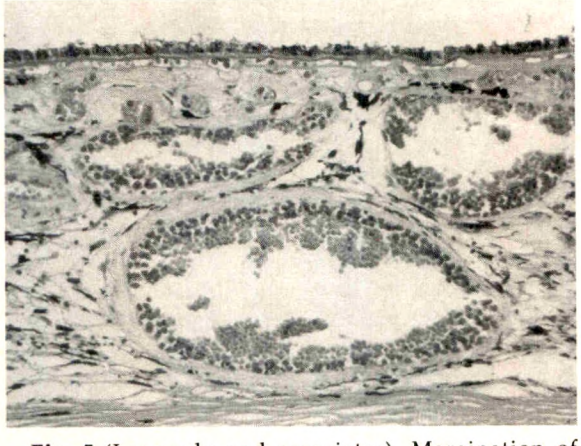

Fig. 5 (Leonardy and associates). Margination of leukemic cells in choroidal vessels (arrows) in acute myeloblastic leukemia (French-American-British Cooperative Group classification Type M2 [acute myeloblastic leukemia with maturation]) (hematoxylin and eosin, × 200).

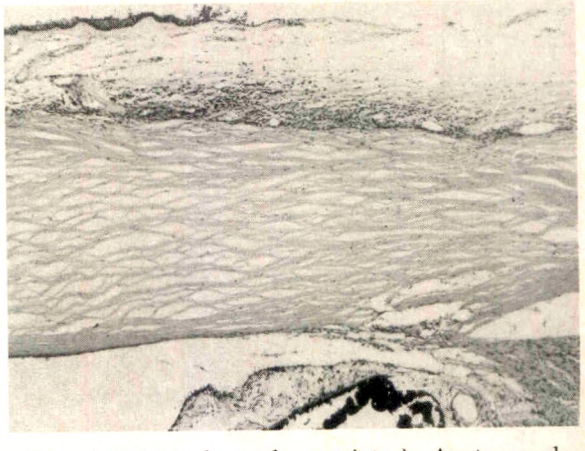

Fig. 6 (Leonardy and associates). Acute myelomonocytic leukemic infiltration in the subconjunctival and anterior episcleral tissue (hematoxylin and eosin, × 68).

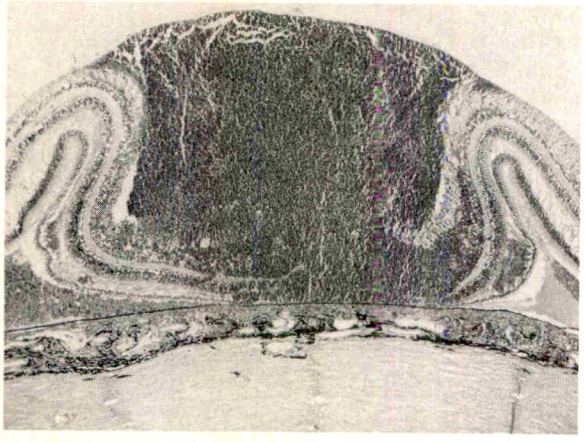

Fig. 7 (Leonardy and associates). Acute lymphoblastic leukemic infiltration of the retina (hematoxylin and eosin, × 40).

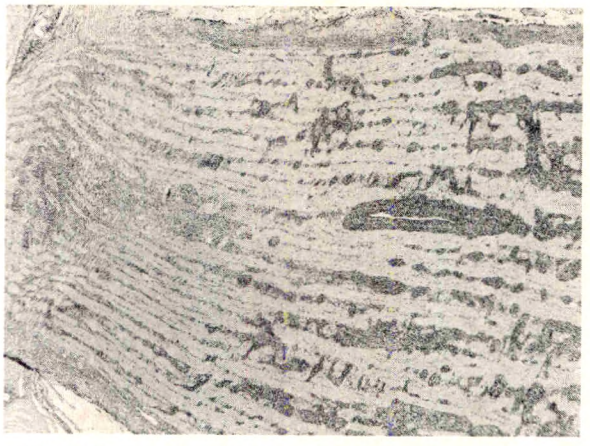

Fig. 8 (Leonardy and associates). Leukemic infiltration (arrows) among the myelinated axons within the optic nerve (hematoxylin and eosin, × 25).

trates in the periocular tissue; all of them except one also had intraocular infiltrates, usually in more than one site. Leukemic cell infiltrates were conspicuous in the retina (Fig. 7), optic nerve (Fig. 8), ciliary body, sclera, and conjunctiva in some eyes. Both patients with leukemia of the optic nerve also had leukemic cell infiltrations in the brain and meninges. In eight eyes, the leukemic cells were present within the choroidal blood vessels, but they were not found extravascularly.

Discussion

The eye and its adnexal tissues may be affected in several ways in individuals with leukemia, and such lesions may be symptomatic. Involvement can result from direct infiltration of the tissues by leukemic cells, and secondary complications such as hemorrhage or infections. Whereas leukemic infiltrates in the eye are common in fatal cases of leukemia, it is questionable whether the disease is a frequent cause of symptomatic ocular lesions. Indeed, only seven patients in our study group had ocular symptoms severe enough to warrant referral to an ophthalmologist. Although the leukemic infiltrates in many patients in our study were extensive, they were not detected clinically, perhaps because detailed ophthalmologic examinations are rarely performed on patients who have terminal cases of leukemia but no severe visual impairment. Even though significant ocular symptoms were uncommon in our study, ocular examination in patients with leukemia may disclose a variety of abnormalities. Symptoms of leukemia apparent on initial examination have included decreased visual activity, vitreous leukemic cell infiltration, and sudden, unilateral visual loss.[2,4,12,13] Retinal lesions found during the course of the leukemic process include hemorrhage, cotton-wool spots, retinal neovascularization, and microaneurysms.[6,9,14,15] Retinal pigment epithelial changes such as atrophy, hypertrophy, and hyperplasia have been reported.[9,16] Leukemia of the iris may produce clinically detectable nodules and heterochromia iridis, and leukemic cells may block aqueous outflow channels, causing an increase of intraocular pressure.[6,17-20] Edema of the optic disk may accompany diffuse leukemic involvement of the central nervous system or leukemic infiltration of the optic nerve head.[21,22] Occasionally, proptosis is a manifestation of myelocytic leukemia (granulocytic sarcoma or chloroma).[3,23,24] The cornea may be involved in leukemia, resulting in corneal ulceration, but leukemic cell infiltration of cornea is rare.[4,25,26]

The reported frequency of ocular leukemic cell infiltrates varies from 28% to 80% (Table 2).[8,9,27,28] In a study of 60 leukemic children, Robb, Ervin, and Sallan[27] detected choroidal leukemic infiltrate in 43% of the patients. Although no correlation between choroidal involvement and the terminal leukocyte count in the peripheral blood was noted, in their study retinal infiltrates were associated with a high leukocyte count in the peripheral blood. In their study, four patients with optic nerve in-

TABLE 2
COMPARISON OF STUDIES ON THE INCIDENCE OF OCULAR INVOLVEMENT IN LEUKEMIAS

INVESTIGATOR	NO. OF PATIENTS	YEARS OF STUDY	INCIDENCE OF OCULAR INVOLVEMENT* IN PATIENTS (%)
Allen and Straatsma (1961)[28]	71	1959–1961	33 of 50 (66)
Robb, Ervin, and Sallen (1979)[27]	60	1968–1977	30–44 of 60† (50–73)
Kincaid and Green (1983)[9]	357‡	1923–1980	284 of 357 (80)
Nelson, Hertzberg, and Klintworth (1983)[8]	117	1973–1982	33 of 117 (28)
Present study (1989)	135	1973–1987	42 of 135 (31)

*Included may be not only ocular involvement by leukemic infiltrates, but also other complications such as hemorrhages. Only patients with leukemia are included; allied disorders, such as plasma cell myeloma, malignant histiocytosis, and lymphoma are not included.

†The precise number of patients is not clear from the publication.

‡The table in this paper indicates 357 patients, but the text indicates 384 patients in four places and 357 patients in two places.

volvement had meningeal leukemia. In an analysis of the eyes of 357 patients (Table 2) with leukemias who underwent autopsy at Johns Hopkins Hospital over a period of 50 years, Kincaid and Green[9] noted ocular involvement in 80% of the cases. They also detected no change in the frequency of leukemic eye involvement over the 57 years covered by their study (1923 to 1980). Nelson, Hertzberg, and Klintworth,[8] however, found ocular leukemic cell infiltrations at autopsy in only 33 (28.2%) of 117 patients who died from leukemia or complications of its treatment.

Several factors may contribute to the variability of the reported incidence of ocular involvement in leukemia. In some studies, the incidence is based only on leukemic infiltrations[8]; others[9,28] have considered leukemic infiltrations and secondary complications. For example, in reporting their data, Kincaid and Green[9] as well as Allen and Straatsma[28] included not only patients with leukemic cell infiltrations of the ocular tissues, but also patients in whom there were other secondary changes, such as retinal hemorrhage without any leukemic cell infiltrations. In the report by Robb, Ervin, and Sallan,[27] 14 of 60 eyes examined were normal. The authors did not describe, however, the abnormalities in the remaining 44 eyes. Another potentially important variable might be the difference in the methods used for investigating the eyes at autopsy. In our study, only one eye was usually processed from each patient, and we often used retinochoroidal scrolls to maximize the area of the retina and choroid available for histologic evaluation. Such scrolls, however, did not disclose significantly more eyes with leukemic infiltrates. Only one eye that did not have leukemic infiltrates in a standard random section contained leukemic infiltrates in the retinochoroidal scroll. An additional factor influencing the incidence of ocular involvement may be the effect of treatment and the amount of residual leukemic infiltrates at the time of death. The extensive series of Kincaid and Green[9] included cases from as early as 1923, before the days of modern chemotherapy, which destroys leukemic infiltrates in tissue as well as circulating leukemic cells. Our cases were biased toward preterminal chemotherapy, and this conceivably accounts at least in part for the lower frequency of ocular leukemic infiltration in our series. Consistent with this possibility was the finding of ocular leukemic infiltrates in five of the seven patients in our study who had no documented chemotherapy. Another factor contributing to differences between series might be the definition of ocular leukemic involvement. Because intravascular cells merely reflect circulating leukocytes, we did not consider eyes to have leukemic cell infiltrations unless the neoplastic cells were noted extravascularly. Nevertheless, intravascular neoplastic cells were uncommon in our series, probably because most of our eyes were obtained after the brain and eyes had been perfused. Additionally, it is unclear whether an occasional possible extravascular leukemic cell should be considered ocular involvement. We encountered 12 such cases in our review, but we did not consider them as indicative of ocular involvement by leukemia because of the diffi-

culty in identifying isolated cells. Even if we include these 12 cases, the incidence of ocular leukemic cell infiltration in our series would only be 40% (54 of 135 patients).

Our study disclosed a positive correlation between the agonal leukocyte count and the presence of ocular leukemic cell infiltration at autopsy (Fig. 1). Leukemic infiltration of the eye also correlated positively with advanced systemic disease as defined by the number of affected organs (Fig. 1). The study of Robb, Ervin, and Sallan[27] demonstrated a relationship between the terminal leukocyte count and the presence or absence of retinal leukemic infiltrates. These positive correlations suggest that ocular manifestations in leukemic patients may indicate advanced disease.

In 1976, a group of French, American, and British hematologists devised a system for classifying acute lymphoblastic and myelogenous leukemias (the French-American-British classification of acute leukemias).[10] This classification[10,29-32] is based on the morphologic characteristics of the cells as seen in Romanovsky-stained preparations and other cytochemical preparations (chloroacetate esterase, alpha-naphthyl acetate esterase, naphthol-AS-D-chloroacetate esterase with and without sodium fluoride incubation, Sudan black B, and myeloperoxidase).

Despite its usefulness, the French-American-British Cooperative Group classification lacks prognostic significance. Recently, the advent of monoclonal antibodies against specific cell antigens has made it possible to categorize acute lymphoblastic leukemias into diagnostically and prognostically useful subtypes with the aid of flow cytometry and immunofluorescence microscopy. A ranking order for prognosis appears to exist for the four major immunologically characterized subtypes of acute lymphoblastic leukemia (> indicates prognosis better than): common acute lymphoblastic leukemia > unclassified acute lymphoblastic leukemia > T cell acute lymphoblastic leukemia > B cell acute lymphoblastic leukemia (in children); and T cell acute lymphoblastic leukemia > common acute lymphoblastic leukemia > unclassified acute lymphoblastic leukemia > B cell acute lymphoblastic leukemia (in adults).[33] Presently, insufficient information is available to prognosticate the immunochemical subgroups of acute myelogenous leukemias.[33]

Chronic leukemias are simply divided into chronic lymphocytic and chronic myelocytic types. Chronic lymphocytic leukemia can be diagnosed clinically when the small, well-differentiated lymphocyte count in the peripheral blood is greater than 15,000 cells/mm^2. Diagnosis of chronic myelocytic leukemia requires a blood leukocyte count greater than 30,000 cells/mm^2 with a full range of myelocytic immaturity and the presence of a specific cytogenetic marker, the Philadelphia chromosome. Bone marrow examination should disclose granulocytic hyperplasia with no more than a moderate degree of fibrosis. If more than 30% of these leukocytes are myeloblasts or promyelocytes, acute myelocytic leukemia or a blast crisis of chronic myelocytic leukemia must be considered.

Some studies have found ocular involvement to be more common in acute than chronic leukemias, but most studies, including ours, detected no significant difference (Table 3). In a prospective two-year clinical study of the ocu-

TABLE 3
INCIDENCE OF OCULAR INFILTRATIONS IN ACUTE AND CHRONIC LEUKEMIA IN DIFFERENT AUTOPSY SERIES

AUTHOR	NO. OF PATIENTS AND INCIDENCE OF OCULAR INVOLVEMENT (%)	
	ACUTE LEUKEMIAS	CHRONIC LEUKEMIAS
Allen and Straatsma[28]	29 of 36 (80.5)	4 of 14 (28.5)
Robb, Ervin, and Sallen[27]	30–44 of 60* (50–73)	—
Kincaid and Green[9]	190 of 233 (82)	73 of 97 (75)
Nelson, Hertzberg, and Klintworth[8]	23 of 86 (26.7)	10 of 31 (32.2)
Present study	32 of 99 (32.3)	10 of 36 (27.8)
Combined studies†	278 of 428 (65)	87 of 147 (59.2)

*The number of patients in the study is not clear.

†The study by Nelson, Hertzberg, and Klintworth is excluded because their data are included in the present, more extensive study.

TABLE 4
LOCATION OF LEUKEMIC DEPOSITS IN EYES INVOLVED BY LEUKEMIA IN DIFFERENT STUDIES

	NO. OF EYES (%)				
LOCATION	PRESENT STUDY*	ROBB, ERVIN, AND SALLEN (1979)[27]	KINCAID AND GREEN (1983)[9]	ALLEN AND STRAATSMA (1961)[28]	COMBINED STUDIES
Choroid	39 of 42 (93)†	26 of 60 (43)	232 of 357 (65)	29 of 33 (88)	326 of 492 (66)
Episclera/sclera	12 of 42 (29)	—	50 of 357 (14)	21 of 33 (64)	83 of 432 (19)
Retina	7 of 42 (17)	8 of 60 (13)	106 of 357 (30)‡	9 of 33 (27)	130 of 492 (26)
Periocular tissues	7 of 42 (17)	—	31 of 357 (9)§	7 of 33 (21)	45 of 492 (9)
Optic nerve	2 of 42 (5)	4 of 60 (7)	51 of 357 (14)	5 of 33 (15)	62 of 492 (13)
Ciliary body	3 of 42 (7)	—	—	7 of 33 (21)	10 of 75 (13)
Conjunctiva	1 of 42 (2)	—	14 of 357 (4)	11 of 33 (33)	26 of 432 (6)
Iris	0 of 42 (0)	—	6 of 357 (2)	2 of 33 (6)	8 of 432 (2)

*Some had infiltrations at more than one site.
†This does not include 12 additional eyes with occasional leukemic cells in the stroma of the choroid.
‡Includes retinal hemorrhages with or without leukemic infiltrations.
§Orbit.

lar manifestations of 53 patients with myeloid leukemia, Karesh and associates[14] found the ocular manifestations to be unrelated to the French-American-British Cooperative Group classification. The presence of retinopathy (cotton-wool spots and hemorrhages) was unrelated to therapeutic responses.

The finding of ocular hemorrhage in 35 of 135 (25.9%) patients underscores the frequency of this complication in leukemia. In other studies, comparable statistics were not determined, although the reported frequency of retinal hemorrhage ranges from 11% to 45%.[9,27,28] In our series, platelet counts did not differ significantly between patients with and without retinal hemorrhage. In a review of 67 leukemic patients, Rubenstein, Yanoff, and Albert[34] also noted that thrombocytopenia alone was not associated with an increased incidence of retinal hemorrhage. In a recent clinical study of 117 consecutive patients with acute leukemia, however, Guyer and associates[35] reported a prospective association between intraretinal hemorrhages and thrombocytopenia.

Leukemic infiltrates may be found in almost any location in the eye. As confirmed in this study, however, they are most frequent in the choroid. In our study 39 of 42 (93%) eyes with leukemic infiltrates had choroidal involvement. The choroid is also the most common site for metastatic carcinoma,[8,36] which probably reflects the choroid's extreme vascularity. That about one third of our patients with posterior choroidal leukemia had perivascular leukemic infiltrates in the anterior episclera is noteworthy. Such involvement did not correlate with any particular type of leukemia. The frequency of leukemic infiltrates in different portions of the eye is summarized in Table 4. No major differences in the distribution of leukemic deposits in the eye were found in the different studies, but compared to other authors, Allen and Straatsma[28] noted a higher frequency of infiltrates in the sclera and episclera (Table 4).

In our series, most individuals with leukemic infiltrates of the central nervous system also manifested them in the optic nerve. This clinically important observation stresses the importance of the ophthalmologic examination for leukemic patients, especially when meningeal involvement is suspected. Takahashi, Oda, and Isayama[21] described leukemic optic neuropathy in seven patients, all of whom had involvement of the brain and meninges. Of the five patients who had leukemic involvement of optic nerve described by Nikaido and associates,[37] three had confirmed central nervous system leukemia, and in two other patients it was strongly suspected. Although most cases of leukemia with optic nerve involvement are of the acute variety, chronic lymphocytic leukemia is also associated with optic infiltrations on rare occasions.[12]

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Bilateral Choroidal Neonatal Neuroblastoma

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We treated a bilateral, well-differentiated neuroblastoma of the choroid in a patient who had congenital abdominal neuroblastoma. Although orbital metastasis of neuroblastoma is common, intraocular metastasis is not. In our patient, there was no amplification of the N-myc oncogene in the tumor of either eye. This is consistent with early-stage primary neuroblastoma. Histologically, the tumors were identical in each eye and well differentiated with Homer Wright rosettes; most neuroblastoma metastases have few rosettes and are composed of more undifferentiated, anaplastic cells. We believe that our patient had bilateral primary tumors and not metastatic tumors.

METASTASES TO THE EYE and orbit are common in tumors in adults; Freedman and Folk[1] estimate that 25,000 patients are affected annually. In the pediatric age group, the most common tumor metastatic to the orbit is neuroblastoma. Albert, Rubenstein, and Scheie[2] found orbital metastasis in 47 of 108 patients with neuroblastoma. No patient, however, had a tumor metastatic to the globe. These authors were unaware of an instance of neuroblastoma metastatic to the choroid.[2]

We have found six published reports of neuroblastomas metastatic to the eye.[1-7] We consider the case described by Bothman and Blankstein[3] to be true tumor infiltration of the choroid and, therefore, to be neuroblastoma metastases, not just tumor cells in choroidal vessels. Their patient was 2½ years of age at time of death. Only one eye was examined histopathologically. Two other cases of choroidal metastasis described in published reports were unilateral, one in an older child,[4] and the other in an adult.[5]

We found two reports of intraocular neuroblastomas presumably metastatic to the iris, one case of which was bilateral.[6,7] The bilateral case, like the present case, was congenital. The tumor was present at birth.

Case Report

Birth was complicated for this infant girl because her abdomen was distended from a tumor involving the liver (Fig. 1). Histologic study showed a neuroblastoma. The tumor was staged as a IV S. Radiation to the abdomen was

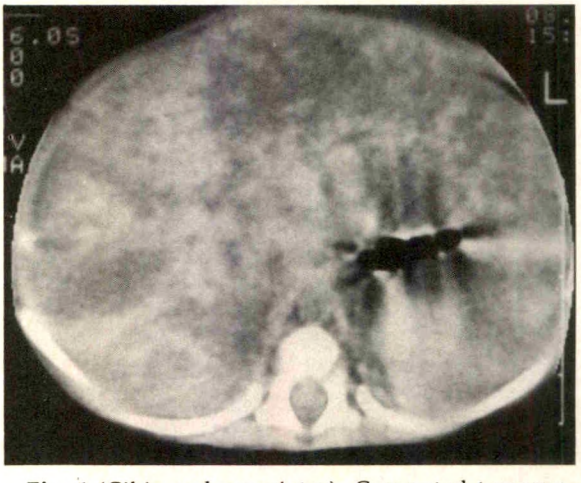

Fig. 1 (Cibis and associates). Computed tomography of abdominal lesion at time of initial examination (age, 1 day).

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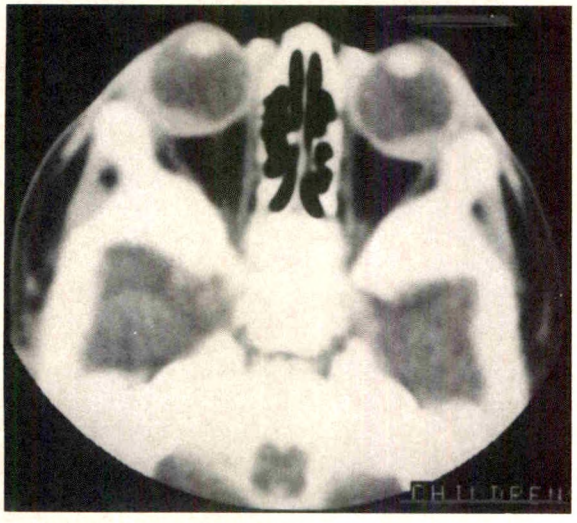

Fig. 2 (Cibis and associates). Computed tomography of globe and orbit showing bilateral intraocular masses (age, 2 months).

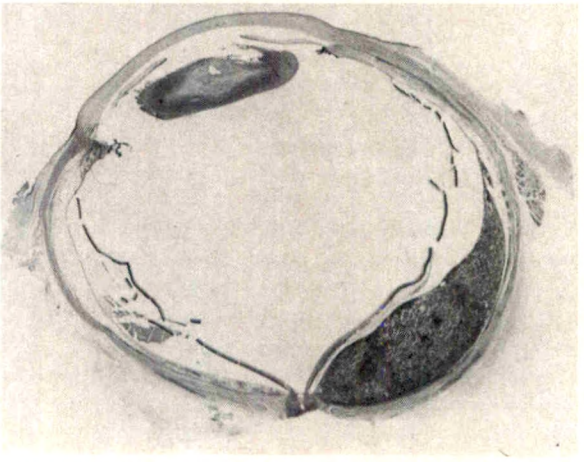

Fig. 3 (Cibis and associates). Light micrograph of the right globe. The choroidal tumor mass is in the area underlying the macula. There is a small nidus of tumor on the opposite side of the optic nerve (× 4).

given on the first five days of life. The treatment successfully reduced liver size and relieved intrathoracic pressure.

The patient was readmitted to the hospital at 2 months of age, and chemotherapy was instituted because of re-expansion of the liver. Proptosis was present, and computed tomography disclosed bilateral intraocular choroidal masses (Fig. 2) and orbital bone involvement. Metastases were seen in bones of the hands and feet, intracranially, and in the lungs. Thus, the patient's condition had evolved to a stage IV.

The patient followed lights and had a positive optokinetic response. An electroretinogram disclosed no abnormalities, and visual-evoked responses were normal in each eye. The ocular tumors appeared to be choroidal on clinical and ultrasonographic examination. The alpha fetoprotein, catecholamine, and vanillylmandelic acid levels were increased, confirming the diagnosis of neuroblastoma.

The patient died at 2½ months of age from tumor progression. The liver and lungs were particularly involved. Autopsy permission was limited to the eyes.

Gross pathologic examination disclosed an anterior posterior length of 23 mm for the right eye and 22 mm for the left eye. Corneas were clear with round pupils. There was a transillumination defect posteriorly in both globes. In both eyes, the vitreous was clear and the lens was in place. A brown tumefaction within each choroid measured 14 mm in diameter in the right eye (elevation, 4 mm), and 11 mm in diameter in the left eye (elevation, 3 mm).

On light microscopy (Figs. 3 to 6), the sclerae were intact in both globes. Abnormalities were limited to a choroidal tumor mass with overlying secondary retinal detachment and pigment epithelial atrophy. The tumor did not involve the retina.

Histologically, the tumors were identical in each eye. The tumor cells were small, round, and uniform in size with large hyperchromatic nuclei, some nucleoli, and scant cytoplasm. Homer Wright rosettes consisting of tumor cells oriented around a central matrix of fibrillar eosinophilic staining material were abundant. Flexner-Wintersteiner rosettes, fleurettes, tumor necrosis, and calcification were not seen. There were few mitotic figures. The tumors appeared well-differentiated.

There was hemorrhage within and on the surface of the tumor as well as in the choroid toward the ora serrata. Tumor cells were seen within choroidal blood vessels. Clinically, the tumor had appeared multifocal, but histologic examination disclosed only one tumor per globe.

Transmission electron microscopy (Fig. 7) showed round, cohesive cells with moderately developed to well-developed desmosomes. The nuclei were large with coarsely clumped and marginated heterochromatin granules. The cytoplasm was composed of the usual cytoplasmic organelles. Many cells displayed elongated cy-

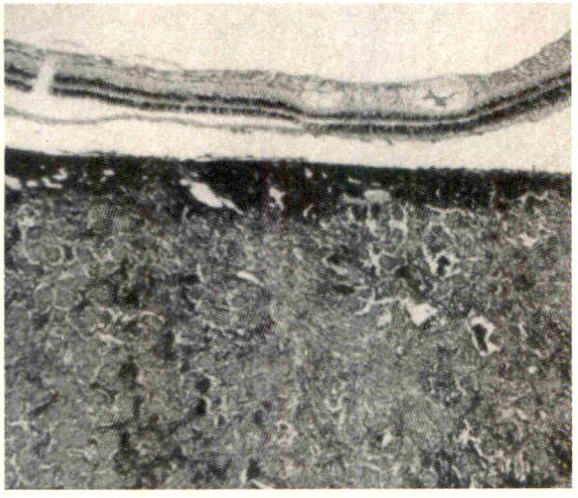

Fig. 4 (Cibis and associates). Right eye. Edge of the tumor mass showing hemorrhage in the choroid. The overlying retina is normal in structure and artifactually detached. There is a true detachment overlying the central portion of the tumor (× 16).

toplasmic processes containing some intermediate filaments. Rare neurosecretory granules were identified (Fig. 7).

The predominance of Homer Wright rosettes, rather than Flexner-Wintersteiner rosettes, the uninvolved retinal layer, the absence of fleurettes, tumor necrosis, and calcification, and the presence of rare neurosecretory granules shown by transmission electron microscopy substantiate the diagnosis of neuroblastoma. Furthermore, the absence of the bullous heads of cytoplasmic processes filled with elongated mitochondria made retinoblastoma unlikely. Thus, light and transmission electron micro-

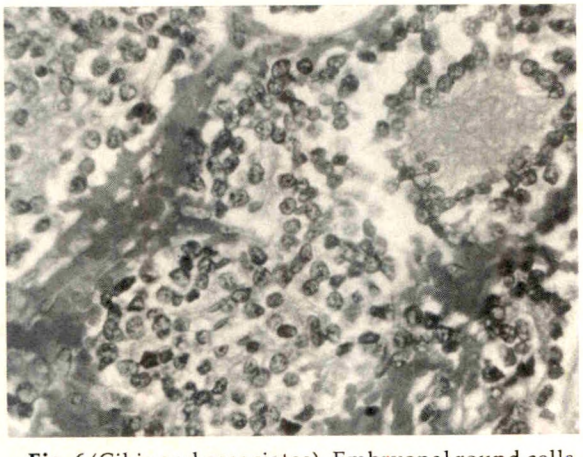

Fig. 6 (Cibis and associates). Embryonal round cells with scant cytoplasm and heavy nuclear chromatin nuclei (× 40).

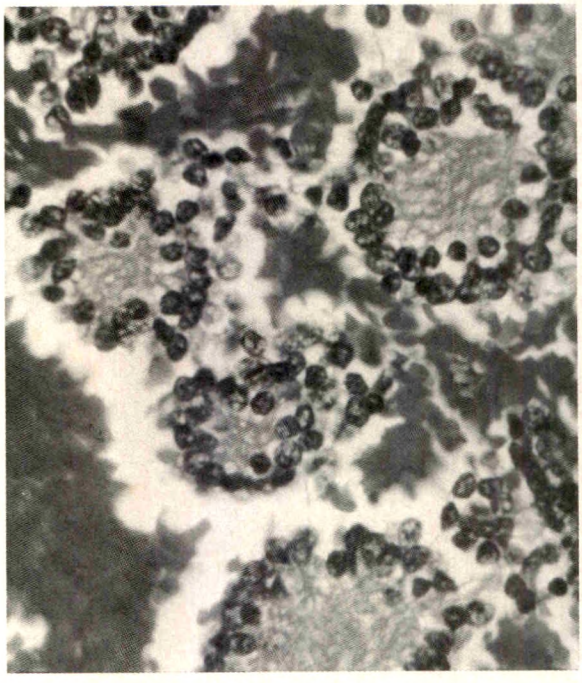

Fig. 5 (Cibis and associates). Light micrograph of the tumor mass showing Homer Wright rosette formation (× 40).

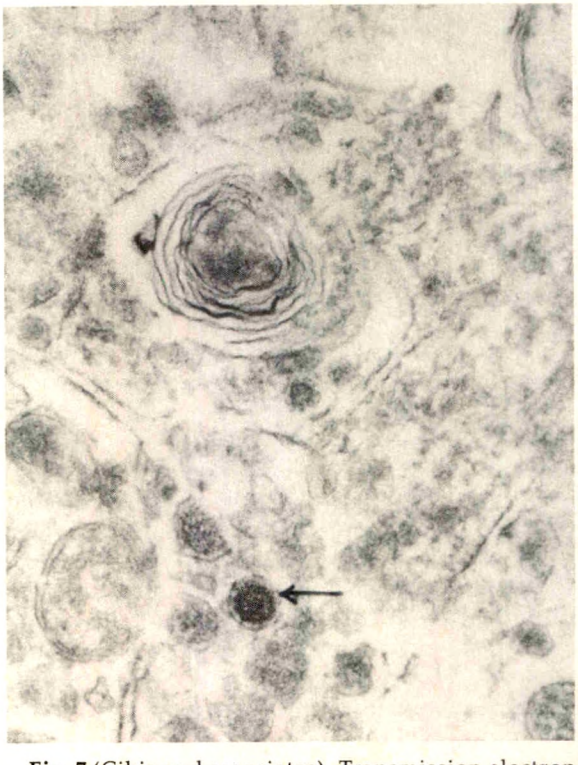

Fig. 7 (Cibis and associates). Transmission electron micrograph shows neurosecretory granule (arrow) (× 31,500).

scopic evidence was consistent with neuroblastoma. Finally, an increased catecholamine level supported the diagnosis of neuroblastoma.

Discussion

Whereas tumors metastatic to the choroid are common in adults,[1,2] they are rare in children. Experimentally, tumor cell emboli are known to lodge anywhere in the eye.[2] Albert, Rubenstein, and Scheie,[2] therefore, suggested that local environmental factors in the child's eye precluded metastatic growth. Two of seven known cases of neuroblastoma within the eye were in the iris, which is an even rarer site of metastasis than the choroid. One of these cases was bilateral, and both were congenital. Therefore, of the three neonatal cases, ours included, two tumors were in the iris and two were bilateral. The congenital nature of three of seven reported cases of intraocular neuroblastoma, including our own, raises the question of multiple primary tumors.

We speculate that congenital bilateral intraocular neuroblastomas with systemic tumors elsewhere are multiple primary tumors, not metastatic tumors, and are an equivalent situation to bilateral or trilateral retinoblastomas. In our case, the well-differentiated nature of the tumors with many Homer Wright rosettes supports this interpretation. Neuroblastomas metastatic to other sites tend to have few rosettes and are composed of more undifferentiated, anaplastic cells. A reported case of esthesioneuroblastoma unilaterally metastatic to the choroid shows these characteristics.[8] Conversely, one may argue that in the newborn, immunologic surveillance may be deficient, allowing more mature tumor cells to metastasize.

Neuroblastomas originate from cells derived from the neural crest. Primitive neuroectodermal tumors, which share that neural crest origin, are histologically indistinguishable but clinically heterogeneous. Such primitive neuroectodermal tumors include esthesioneuroblastoma, adult neuroblastoma, and adrenal neuroblastoma of early childhood. Neonatal neuroblastomas with intraocular involvement must be investigated with modern cytogenetic and molecular genetic techniques to provide a rational basis for biologic classification and therapy.[9]

The two-mutation model of tumorigenesis has been applied to neuroblastoma as well as retinoblastoma.[10] Using statistical analysis of age-clustering in tumor patients, Knudson and Meadows[10] postulated that two independent mutations are needed for a cell to become malignant. In patients with inherited neuroblastoma, the first mutation is prezygotic; all cells are therefore involved. Only a mutation in the remaining normal allele in a susceptible cell is needed for cancer to develop. Such a mutation increases the probability of tumor by 10,000 to 100,000 times. The early (congenital) incidence of the present case is consistent with an inherited neuroblastoma. Multiple primary tumors are also consistent with inherited tumor. Thus, the present case is likely to be an inherited neuroblastoma.

The oncogenes are a group of approximately 40 genes that have been implicated in causing neoplastic transformation. These genes are normal constituents of the genome. The normal functions of most members of this group are unclear, although some oncogenes appear to be similar or identical to certain growth factors and growth factor receptors.[9] Disturbances in the structure or regulation of expression, or both, of these genes is a frequent finding in cancer. For example, the c-myc oncogene is rearranged in Burkitt's lymphoma.[11] The myc family of oncogenes code for protein products that are located in the nucleus, where they presumably are involved in controlling the expression of other genes.[12,13] The Burkitt's lymphoma rearrangement brings one of the immunoglobulin genes in proximity to c-myc and disrupts its normal regulation.

In neuroblastoma, no alteration of oncogene structure or regulation is consistently found. The oncogene N-myc, however, is implicated in a subset of neuroblastoma.[9,11-15] Amplification, or the abnormal presence of excess copies, of the N-myc gene has been associated with advanced-stage neuroblastoma and poor prognosis within each stage of neuroblastoma. The N-myc gene has some structural similarities to the c-myc gene described but is a distinct gene. The function of the N-myc gene is unknown, but a higher level of expression is found in immature neuroblasts, and chemically induced differentiation of neuroblastoma cells in vitro has been shown to correlate with a reduction in expression of the N-myc gene.[16,17] Amplification of the N-myc gene presumably interferes with the reduction in expression expected during differentiation and may actually block differentiation of neuroblastoma cells in vivo.[18] This could possibly account for the worse prognosis of neuroblastoma with N-myc amplification.

In the present case, when formalin-fixed, par-

affin-embedded tissue was analyzed, there was no amplification of N-myc in either ocular tumor. The absence of N-myc amplification in these choroidal neuroblastomas is consistent with early-stage primary neuroblastoma.

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G. M. Brodeur, M.D., Departments of Pediatrics and Genetics, Washington University School of Medicine, St. Louis, Missouri, performed the genetic analysis of ocular tissue.

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Ocular and Systemic Findings in the Aarskog (Facial-digital-genital) Syndrome

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The Aarskog (facial-digital-genital) syndrome is an X-linked disorder in which short stature is accompanied by hypertelorism, digital anomalies, and shawl scrotum. Except for hypertelorism and blepharoptosis, ophthalmic abnormalities have been rarely noted in this condition. We examined four patients who had Aarskog syndrome and unilaterally or bilaterally decreased vision on initial examination. Three family members had V-pattern esotropia, latent nystagmus, inferior oblique overaction, and amblyopia. A fourth patient had bilateral blepharoptosis and severe astigmatism. Other ocular features included hyperopia, anisometropia, deficient ocular elevation, blue sclerae, and posterior embryotoxon. These findings underscore the need for ophthalmic examination in asymptomatic patients with Aarskog syndrome to rule out treatable causes of visual loss.

In 1970, Aarskog described seven males from two generations of a Norwegian family with a syndrome of short stature, hypertelorism, blepharoptosis, round face, small hands, and shawl scrotum.[1] He believed that the disorder was transmitted in an X-linked, recessive mode, noting that carrier women in the pedigree tended to be short. Subsequently, numerous pedigrees have been described, with full expression of the syndrome in affected males and minimal expression in females. This distinct clinical entity is now known as the Aarskog syndrome or the facial-digital-genital syndrome.

The most consistent clinical manifestations of Aarskog syndrome are short stature, hypertelorism, blepharoptosis, short anteverted nares, joint laxity, inguinal hernia, shawl scrotum, cryptorchidism, pectus excavatum, and vertebral anomalies.[2] Intelligence is usually normal, although developmental delay and mild mental retardation have been noted in occasional patients. Ophthalmologic signs, in addition to hypertelorism and blepharoptosis, include antimongoloid slanting of the palpebral fissures,[1] strabismus,[3-6] ophthalmoplegia,[7,8] blue sclerae,[9] and corneal enlargement.[3] Most reported pedigrees have been consistent with an X-linked mode of inheritance; however, autosomal-dominant transmission has been observed in two families,[10,11] which suggests genetic heterogeneity in the Aarskog syndrome.

We examined four patients who had Aarskog syndrome and emphasize the high prevalence of unrecognized strabismus, amblyopia, and astigmatism in this condition.

Case Reports

Case 1

A 4½-year-old boy with Aarskog syndrome and no history of strabismus was referred to us for routine eye examination. As an infant, he had surgical repair of an anteriorly displaced anus. He had several staring spells in the first two years of life, suggesting a possible seizure disorder. His I.Q. was 74, and his height and weight were below the fifth percentile for his age.

The patient had a round face, broad forehead, short stubby nose with anteverted nares, and

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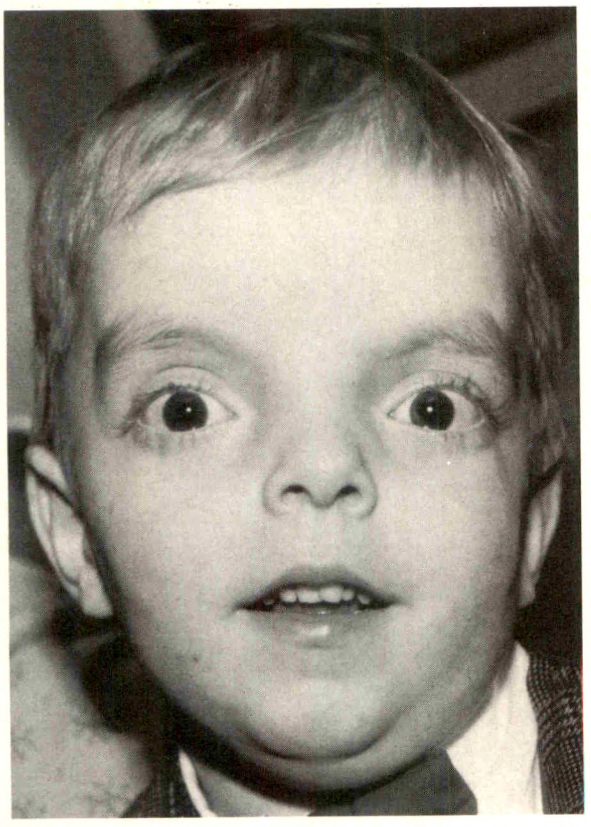

Fig. 1 (Brodsky and associates). Patient 1. Note round face, broad forehead, hypertelorism, telecanthus, short nose with anteverted nostrils, long philtrum, and low-set ears.

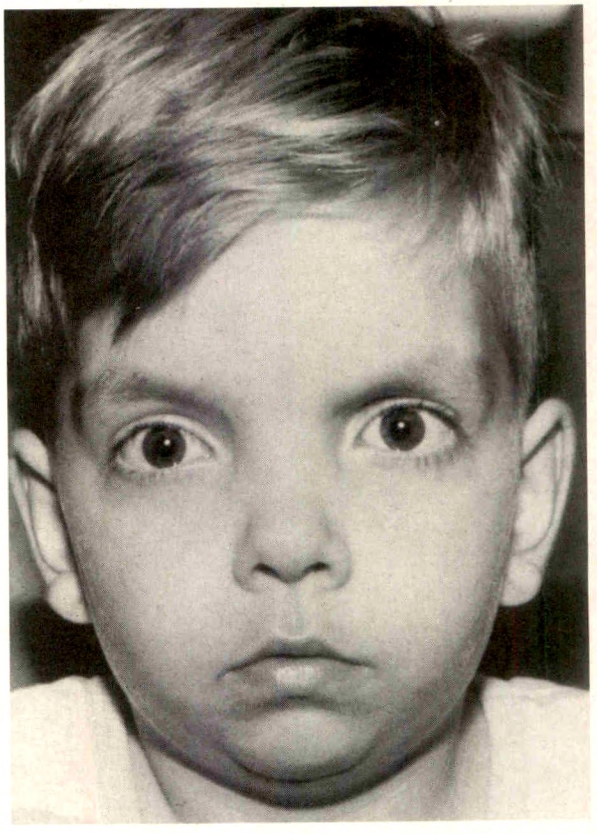

Fig. 2 (Brodsky and associates). Patient 2 (brother of Patient 1). Note round face, broad forehead, mild hypertelorism and telecanthus, short nose, long philtrum producing V-shaped indentation in upper lip, full, pouty, lower lip with curved depression just below it, and low-set ears.

long philtrum, which are typical features in this condition (Fig. 1). He had obvious hypertelorism and telecanthus (interpupillary distance, 60 mm; inner canthal distance, 35 mm; and outer canthal distance, 95 mm). His ears appeared low-set, and the right ear was posteriorly rotated. He had a shawl scrotum and bilateral inguinal hernias.

Corrected visual acuity was R.E.: 20/100, L.E.: 20/200, and 20/40 with both eyes open. The patient appeared orthotropic but measured 15 prism diopters of esotropia fixing at near. He had latent nystagmus and moderate overaction of the inferior oblique muscles. The sclerae showed a uniform blue discoloration. Refractive error was +4.25 + 0.75 × 75 in the right eye and +5.50 in the left eye. When given his full cycloplegic refraction, he had no residual esotropia. His amblyopia resolved with full-time occlusion of the right eye.

Case 2

The 5½-year-old brother of Patient 1 was examined in a genetics clinic for Aarskog syndrome, a urology clinic for cryptorchidism, a dental clinic for multiple caries, and an ophthalmology clinic for esotropia, anisometropia, and amblyopia. He had generalized developmental delay as an infant, and his I.Q. was 72. His height and weight were below the fifth percentile for his age.

Facial features included a round face, broad forehead, short nose, long philtrum, full, pouty lower lip with a curved depression just below it, and low-set ears (Fig. 2). Hypertelorism and telecanthus were less pronounced than in his brother (interpupillary distance, 55 mm; inner canthal distance, 32 mm; and outer canthal

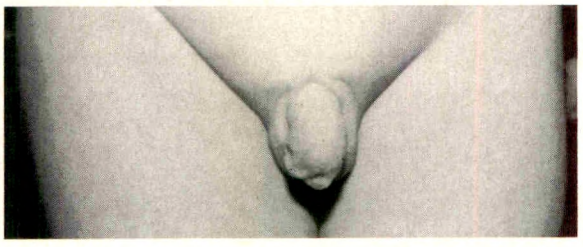

Fig. 3 (Brodsky and associates). Patient 2. Note scrotal folds extending ventrally around the base of the penis (shawl scrotum).

distance, 90 mm). His fingers were slightly short, and his thumbs and toes were broad. He had a shawl scrotum (Fig. 3), cryptorchidism, and bilateral inguinal hernias.

Corrected visual acuity was R.E.: 20/30 and L.E.: 20/50. He had 25 prism diopters esotropia fixing at distance and 30 prism diopters esotropia fixing at near, with a V-pattern. His full hyperopic correction reduced his esotropia to 14 prism diopters at distance and 18 prism diopters at near. He had latent nystagmus, dissociated vertical deviation, and marked overaction of the inferior oblique muscles. Cycloplegic refraction was +3.00 + 1.25 × 80 in his right eye and +5.50 + 1.00 × 90 in his left eye. The retinas were normal.

After successful occlusion therapy for amblyopia, the patient underwent bilateral medial rectus muscle and inferior oblique muscle recessions. At surgery, extraocular muscles were normally positioned. Light microscopic examination of an inferior oblique muscle biopsy specimen showed no abnormalities. Six months postoperatively, the patient was orthotropic at distance and near without residual V-pattern.

Case 3

The 30-year-old mother of Patients 1 and 2 had poor vision in the right eye since childhood but denied a history of strabismus. As a child, she was notably shorter than her siblings. Her adult height was 4 feet 11 inches. Except for the two sons with Aarskog syndrome (Patients 1 and 2), there were no other affected family members. The patient's facial features included hypertelorism and telecanthus (interpupillary distance, 68 mm; inner canthal distance, 40 mm; and outer canthal distance, 97 mm), round face, short stubby nose, and long philtrum (Fig. 4). She had no digital or genital abnormalities.

Fig. 4 (Brodsky and associates). Patient 3 (mother of Patients 1 and 2). Note mild manifestations of Aarskog syndrome, including round face, broad forehead, mild hypertelorism and telecanthus, mild left upper eyelid blepharoptosis, short nose, and long philtrum.

Corrected visual acuity was R.E.: 20/200, L.E.: 20/40, and 20/30 with both eyes open. She had 25 to 30 prism diopters V-pattern esotropia at distance and near fixation. She had moderate inferior oblique muscle overaction, latent nystagmus, and a right dissociated vertical deviation. A mild left upper eyelid blepharoptosis was evident. Levator muscle function was 14 mm in both eyes. Slit-lamp examination showed posterior embryotoxon in both eyes. Refractive error was +1.00 + 2.25 × 114 in the right eye and +0.25 + 1.00 × 129 in the left eye. The retinas were normal.

Case 4

A 5½-year-old boy with Aarskog syndrome was referred to us for the evaluation of bilateral congenital blepharoptosis. Intellectual devel-

Fig. 5 (Brodsky and associates). Patient 4 (unrelated to Patients 1 to 3). Note round face, broad forehead, hypertelorism, telecanthus, moderate bilateral upper eyelid blepharoptosis, short stubby nose with anteverted nostrils, long philtrum, thin upper lip, and low-set ears.

opment was above average; however, height, weight, and head circumference were below the third percentile for his age. He had hypertelorism, telecanthus, and antimongoloid palpebral fissures (Fig. 5). Interpupillary distance was 55 mm, inner canthal distance was 35 mm, and outer canthal distance was 85 mm. He had a broad nasal bridge, a short nose, and a long philtrum that produced a V-shaped indentation in the upper lip. There was mild maxillary hypoplasia. His ears were thick, low-set, and posteriorly rotated with simple helices (jug-handle ears). He had short stubby fingers with mild interdigital webbing (Fig. 6) and hyperextensibility of the proximal interphalangeal joints. There was pectus excavatum and a protruding umbilicus. The scrotal folds encircled the base of the penis.

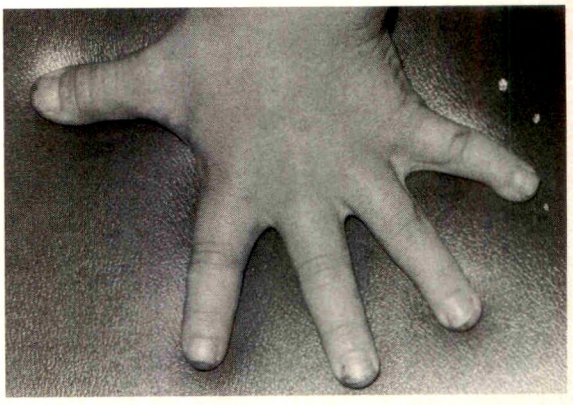

Fig. 6 (Brodsky and associates). Patient 4. Note short stubby fingers with interdigital webbing.

Uncorrected visual acuity was 20/80 bilaterally. There was severe bilateral upper eyelid blepharoptosis (Fig. 5). Palpebral fissure width measured 6 mm in both eyes, levator muscle function was 3 mm in the right eye and 5 mm in the left eye, and eyelid creases were 5 mm in both eyes. Upgaze was limited to 15 to 20 degrees above primary gaze. All other ductions were full. The patient had no strabismus. Refractive error was $-1.25 + 3.50 \times 90$ in the right eye and $-0.50 + 4.00 \times 90$ in the left eye. Corrected visual acuity was 20/25 in each eye. Results of slit-lamp and retinal examinations were normal.

We performed bilateral levator muscle resections (15 to 18 mm in the right eye, 12 to 15 mm in the left eye). At surgery, the levator muscle aponeurosis appeared thin and atrophic. Postoperatively, the patient had 9-mm palpebral fissures and symmetric eyelid contour bilaterally, with no residual blepharoptosis (Fig. 7). Deficient elevation of both eyes persisted after surgery for blepharoptosis.

Discussion

Aarskog syndrome is a genetic disorder characterized by multiple facial, digital, and genital anomalies that constitute a distinct phenotype. The cardinal features are short stature, hypertelorism, digital anomalies, and shawl scrotum. Affected males are usually short,[11] but they may experience a growth spurt in the late teens, resulting in adult height in the low-to-normal range.[12] No endocrine basis for the short stature

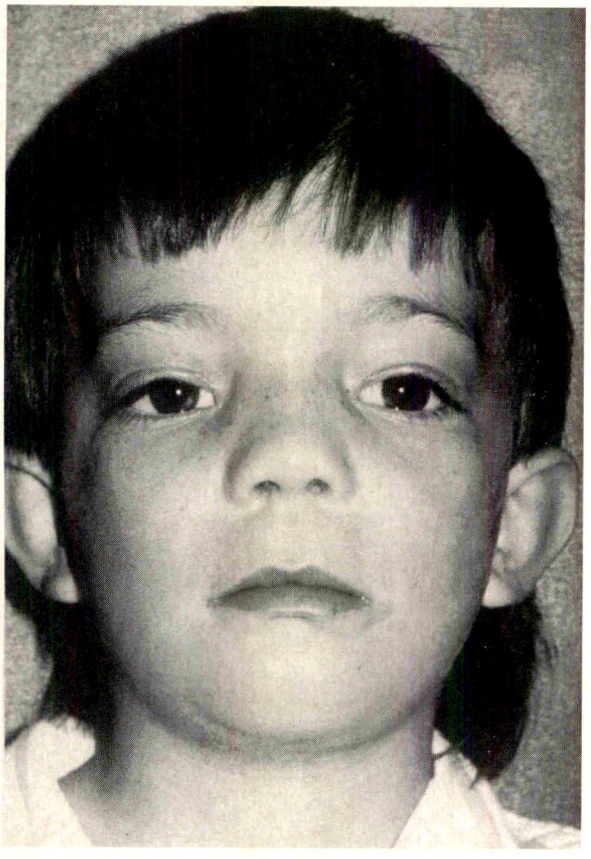

Fig. 7 (Brodsky and associates). Patient 4 after bilateral levator resection. Note improved eyelid position with symmetric contour.

has been found.[7,12] The face is typically round, with a prominent forehead. There is hypertelorism, variable blepharoptosis, and antimongoloid slanting of the palpebral fissures. The nose is short and stubby with a broad nasal bridge and anteversion of the nostrils. There is maxillary hypoplasia, and a long philtrum that forms a deep V in the upper lip.[13] The lower lip is full, with a horizontal groove directly below it.[13] The ears are often low-set and protuberant, with fleshy superior and simple lower helices (jug-handle ears).[13] Digital anomalies include broad and short fingers, interdigital webbing, clinodactyly (incurving of the fifth digit), and hyperextensibility of the proximal interphalangeal joints with concomitant flexion of the distal joints. Genital examination shows bifid or cleft scrotum, with scrotal folds extending ventrally over the base of the penis (shawl scrotum), often accompanied by cryptorchidism and inguinal hernia. Affected females exhibit milder clinical manifestations but have no genital anomaly. Aarskog syndrome in females is attributed to nonrandom inactivation of an X-chromosome (lyonization)[2,6] or to autosomal-dominant inheritance.[13]

Children with Aarskog syndrome are typically examined in genetics clinics for dysmorphic features, in urology clinics for inguinal hernia or cryptorchidism, and in endocrine clinics for short stature.[13] Unless severe congenital blepharoptosis is present, ophthalmic consultation is not routinely sought. Of 105 cases of Aarskog syndrome described in nonophthalmic published reports, only three patients with strabismus have been identified.[4-6] Kirkham, Milot, and Berman[3] studied ophthalmic abnormalities in four patients who had Aarskog syndrome, and they found V-pattern intermittent exotropia with latent nystagmus in one patient, and bilateral Brown's tendon sheath syndrome, esotropia, and amblyopia in another patient. The high prevalence of strabismus and amblyopia in our patients and in Kirkham, Milot, and Berman's[3] patients contrasts sharply with the low prevalence described in the pediatric and genetic literature.

The most striking ophthalmic finding in our study was V-pattern esotropia in three family members with Aarskog syndrome. This was accompanied by latent nystagmus and bilateral inferior oblique muscle overaction in all three patients, dissociated vertical deviation in two patients, and hyperopia in two patients. This constellation of findings may comprise an expanded set of abnormalities in the Aarskog syndrome; however, an unrelated familial predisposition cannot be ruled out without further investigation. The angle of esotropia varied from 15 to 30 diopters at near fixation, and all patients had amblyopia. Patients 1 and 3 had strabismic amblyopia, whereas in Patient 2, the anisometropia was of sufficient magnitude to cause amblyopia. Ocular alignment was restored with hyperopic spectacles in one patient (Patient 1), and with medial rectus muscle and inferior oblique muscle recessions in another patient (Patient 2). In all three family members, esotropia went unnoticed by parents and physicians until ophthalmic examination was performed. As seen in Figures 1, 2, and 4, the eyes of all esotropic patients appeared cosmetically straight. Because hypertelorism may produce an appearance of exotropia, it is not surprising that small-angle esotropia was inconspicuous.

In our series, one patient had severe bilateral blepharoptosis and another had moderate unilateral blepharoptosis. This is consistent with the 44% incidence of blepharoptosis reported in previous studies.[1-28] Of 21 cases in which specific information is available, 13 patients had bilateral blepharoptosis and eight had unilateral blepharoptosis.[1-5,12,14,21,26,28] The cause of blepharoptosis in Aarskog syndrome is unknown. A biopsy specimen of one patient showed absence of striated muscle and an abundance of mast cells. All four patients described by Kirkham, Milot, and Berman[3] had blepharoptosis with levator muscle function ranging from 0 to 10 mm.[3] The choice of surgical procedure, therefore, varies from levator muscle resection in patients with mild-to-moderate blepharoptosis, to frontalis sling or maximal levator muscle resection in patients with absent or minimal levator muscle function. Our patient's blepharoptosis was successfully treated with standard levator muscle resection.

Hypertelorism and primary telecanthus were present in three patients and possibly present in another patient. Hypertelorism is defined as increased distance between the medial orbital walls,[29] and can be shown radiographically or clinically by an increase in interpupillary distance. We defined hypertelorism as interpupillary distance greater than two standard deviations above the mean for the patient's age, using standard anthropometric tables.[30] Telecanthus refers to a widened distance between the inner canthi, and was identified if the Mustarde index (ratio of inner canthal distance to interpupillary distance) was greater than 0.55.[31]

Additional findings included impaired upgaze in one patient with bilateral blepharoptosis, blue sclerae in one patient, astigmatism in two patients, and posterior embryotoxon in one patient. Impaired upgaze has not been noted in previous Aarskog patients; however, ophthalmoplegia has been previously observed in four patients.[7,8] Blue sclerae have been reported in five members of a single pedigree.[9]

We were impressed by the finding of reduced vision in all patients on initial examination. The high prevalence of small-angle esotropia, amblyopia, anisometropia, and astigmatism in our patients underscores the need for ophthalmic examination in asymptomatic patients with Aarskog syndrome.

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OPHTHALMIC MINIATURE

Ondine stopped plucking and lifted her eyes slowly to the place where the window shutters did not quite close. A bit of the sky was unhidden by foliage. She thought she heard a small, smooth sound, like a well-oiled gear shifting. Not a sound really—more of an imagined impression, as though she were a dust mote watching an eye blink. There would be the hurricane wind of eyelashes falling through the air and the weighty crash of lid on lid.

Toni Morrison, *Tar Baby*
New York, Signet, 1983, p. 82

Electroretinograms in Microcephaly With Chorioretinal Degeneration

Francis J. Manning, M.D., Amanda M. Bruce, B.S., and Eliot L. Berson, M.D.

We recorded full-field electroretinograms from a family with two daughters with microcephaly and chorioretinal degeneration and a third daughter and mother with microcephaly without chorioretinal degeneration. The two siblings with inferior chorioretinal degeneration showed electroretinographic responses to 0.5-Hz white light that were reduced 60% to 70% below normal, suggesting that the loss of photoreceptor function exceeded the areas of visible atrophy. The mother and third daughter had normal electroretinograms. The two siblings, ages 12 and 21 years, had virtually the same electroretinographic amplitudes. In a second family, a man with microcephaly and inferior chorioretinal degeneration, examined at ages 9 and 23 years, also showed 60% to 70% reduction in electroretinographic responses to 0.5-Hz white light and showed no change in amplitudes over the 14-year interval. These findings suggest that the chorioretinal degeneration sometimes associated with microcephaly is stable in young adult life, although the long-term prognosis remains to be defined.

PATIENTS have been considered microcephalic if their head circumferences are more than two standard deviations below the mean head circumference of normal subjects after correcting for age and sex.[1,2] Familial microcephaly is inherited in an autosomal-dominant[3-5] or autosomal-recessive[5,6] mode with or without other malformations.[7,8] Those with dominantly inherited microcephaly usually have normal stature and borderline normal intelligence but may show a receding forehead.[3] Those with recessively inherited microcephaly typically have short stature, severe mental retardation, seizures, and other neurologic abnormalities; they have an acutely receding forehead, hypoplastic chin, and prominent nose and ears.[3] Microcephaly can also be acquired in utero after exposure to agents such as *Toxoplasma* species, cytomegalovirus, thalidomide, and radiation.[9-12] In both hereditary and acquired microcephaly, maldevelopment of the brain precedes and precipitates closure of the cranial sutures and, therefore, microcephaly is thought to reflect a primary developmental abnormality in neural tissue.[13]

The association between microcephaly and ocular anomalies is well known.[14-23] Microphthalmia, microcornea, strabismus, nystagmus, myopia, choroidal and disk colobomata, cataracts, and optic nerve atrophy have been described in relation to microcephaly inherited in an autosomal-recessive mode.[14,16-20] Chorioretinal degeneration has been reported primarily in association with recessively inherited microcephaly,[18-21] but it has also been described without other ocular abnormalities in families with dominantly inherited microcephaly.[22,23] The chorioretinal degeneration has been characterized by attenuated retinal vessels and abnormal clumps of pigment at the level of the retinal pigment epithelium surrounding equatorial round areas of chorioretinal atrophy. The electroretinogram has been reported to be reduced in amplitude in cases of microcephaly with chorioretinal degeneration,[17] but the electroretinograms were not subdivided into rod and cone components nor were the implicit times considered. Electroretinograms from the same patient over time have yet to be reported.

We recorded full-field electroretinograms from one family with two daughters with microcephaly and chorioretinal degeneration, and

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a third daughter and mother with microcephaly without chorioretinal degeneration. We evaluated the rod and cone components of their responses for amplitudes and implicit times. We also evaluated full-field electroretinograms over a 14-year interval from a man with microcephaly and chorioretinal degeneration from another family to obtain information on the course of this chorioretinal degeneration.

Case Reports

The ages and head circumferences of the patients studied are summarized in the Table. The normocephalic father from Family 1 had normal ocular examination results, including a normal final rod dark adaptation threshold in the Goldmann-Weekers adaptometer with an 11-degree white test light fixated 7 degrees above the fovea and normal color vision on the Farnsworth D-15 panel. The mother from Family 1 had microcephaly, but the results of her ocular examination were normal. The parents denied consanguinity and reported that the pregnancies and deliveries of their three daughters with microcephaly were uneventful. All three daughters had receding foreheads; the third daughter's I.Q. test reflected borderline normal intelligence. For the other daughters, results of I.Q. tests were not available.

Case 1

Ophthalmic examination of the first daughter from Family 1 disclosed best-corrected visual acuity of R.E.: 20/200 and L.E.: 20/70. Refractive error was $-2.00 - 0.25 \times 28$ degrees in the right eye and $-0.50 - 1.25 \times 145$ degrees in the left eye. Her irides, lenses, and ocular tensions were normal. Fundus examination of each eye showed a disk with slight temporal pallor, slightly attenuated retinal arterioles, granular macula, and an inferior zone of chorioretinal atrophy with clumped pigment at the level of the retinal pigment epithelium (Fig. 1, top). Dark adaptation testing with the Goldmann-Weekers adaptometer disclosed a final rod threshold within normal limits fixating centrally. Visual field testing showed an extensive superior midperipheral scotoma in each eye with a V_{4e} white test light. Color vision testing on the Farnsworth D-15 panel suggested a tritan axis of confusion. Fluorescein angiography showed an absence of filling of the choriocapillaris with no leakage in the areas of chorioretinal degeneration. No antibodies to *Toxoplasma* or rubella were detected. Chromosomal analysis of blood showed a normal karyotype. A computed tomographic scan disclosed no intracranial abnormalities.

TABLE

HEAD CIRCUMFERENCES IN PATIENTS WITH MICROCEPHALY

	AGE (YRS)	HEAD CIRCUMFERENCE (CM)	NORMAL RANGE* (CM)
Family 1			
Father	50	58.0	53.5–59.5
Mother	47	52.0	52.5–58.5
Daughter 1	21	50.5	52.0–58.0
Daughter 2	18	49.5	52.0–58.0
Daughter 3	12	50.0	50.5–56.5
Family 2			
Man	23	49.5	53.0–59.0

*Designates normal range (two standard deviations above and below the mean) of head circumferences in centimeters for age and sex.[2]

Case 2

Patient 2, the second daughter, had best-corrected visual acuity of R.E.: 20/20 − 3 and L.E.: 20/25 − 3; her refractive error was $+1.75 - 1.00 \times 135$ degrees in the right eye and $+3.25 - 1.00 \times 50$ degrees in the left eye. Irides, lenses, and ocular tensions were normal. Fundus examination showed a normal disk, macula, vessels, and fundus periphery in each eye. Final rod dark adaptation threshold, color vision, and visual fields were normal.

Case 3

Patient 3 had best-corrected visual acuity of R.E.: 20/100 and L.E.: 20/100 − 2; her refractive error was $-1.00 + 1.50 \times 90$ degrees in the right eye and $-1.00 + 1.50 \times 90$ degrees in the left eye. Irides, lenses, and ocular tensions were normal. Results of the fundus examination (Fig. 1, middle) of each eye were comparable to those seen in Patient 1. Dark adaptation testing showed a normal final rod threshold fixating centrally, and color vision testing on the Farnsworth D-15 panel suggested a tritan axis of confusion. Visual field testing showed a superior midperipheral scotoma in each eye to a V_{4e} white test light. Fluorescein angiography showed no unusual leakage of dye in the areas of chorioretinal atrophy.

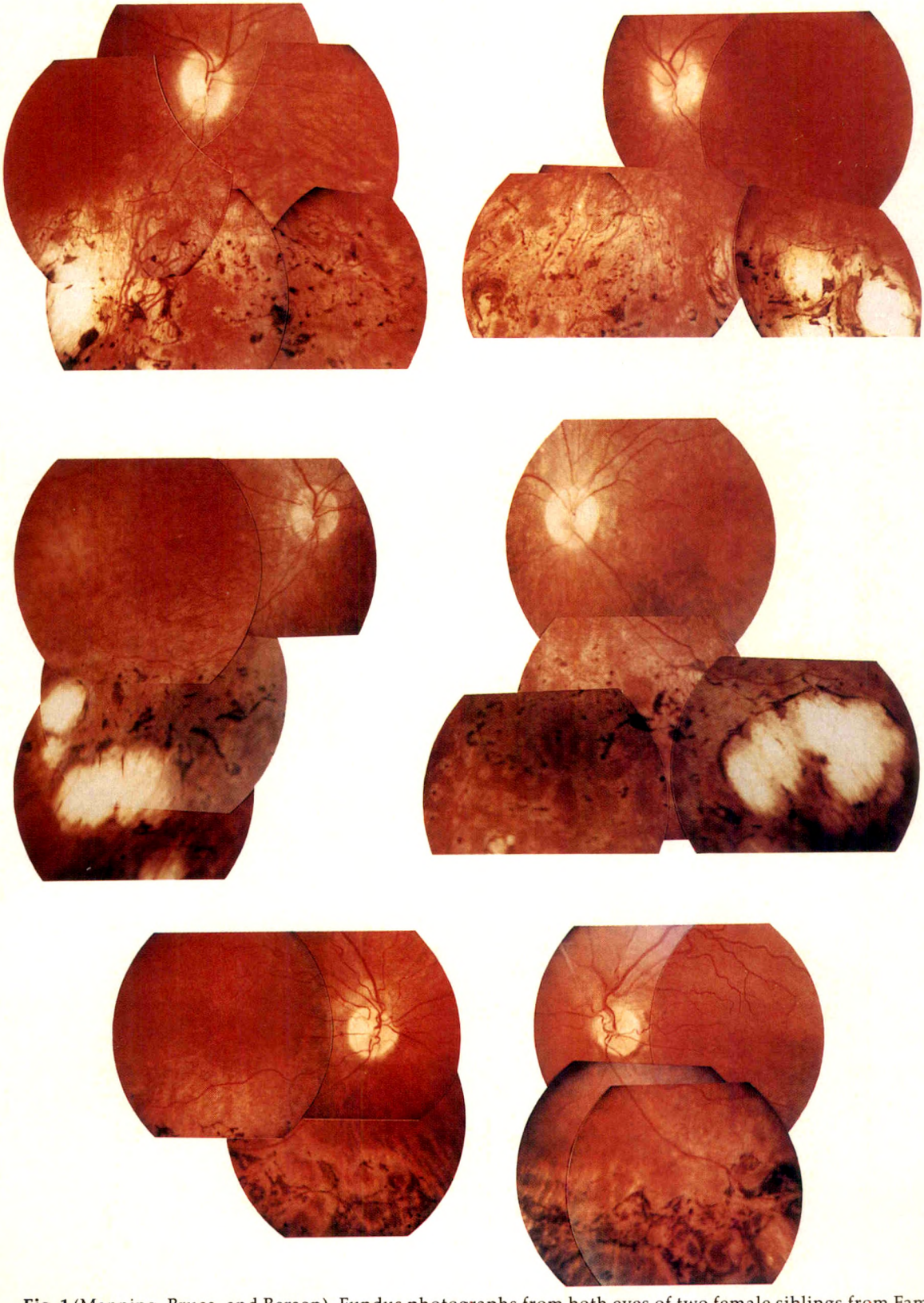

Fig. 1 (Manning, Bruce, and Berson). Fundus photographs from both eyes of two female siblings from Family 1 (Patients 1 and 3, top and middle) and an unrelated man from Family 2 (bottom) with microcephaly and inferior chorioretinal degeneration. For each patient, comparable changes were seen in both eyes.

Case 4

An unrelated man with microcephaly from Family 2 had a best-corrected visual acuity of 20/30 in each eye; his refractive error was −0.75 in the right eye and −0.75 − 1.00 × 80 degrees in the left eye. His irides, lenses, and ocular tensions were normal. Fundus examination of each eye showed a normal disk and macula, slightly attenuated retinal arterioles, and inferior chorioretinal atrophy with clumped pigment deposition at the level of the retinal pigment epithelium (Fig. 1, bottom). Final rod threshold was within normal limits. Results of color vision testing on the Farnsworth D-15 were normal. Visual field testing showed a superior midperipheral scotoma in each eye to a V_{4e} white test light. Fluorescein angiography showed no evidence of leakage of dye in the areas of chorioretinal atrophy. Chromosomal analysis of blood showed a normal karyotype. Features apparent on a skull x-ray were consistent with microcephaly and showed no intraorbital or intracranial calcifications. Both orbits were normal in size and configuration. A *Toxoplasma* titer was negative. The patient's mother had a head circumference of 54 cm with normal ocular findings. His father had normal vision and was normocephalic by history; further information on ocular findings was not available.

Full-field (ganzfeld) electroretinograms were recorded as described previously.[24-30] Rod-isolated responses were elicited to single flashes (0.5 Hz) of dim blue light (1.2 log ft-L, γ_{max} = 440 nm), mixed cone-rod responses to single flashes (0.5 Hz) of white light (3.8 log ft-L), and cone-isolated responses to 30-Hz white flicker (3.8 log ft-L). Peak-to-peak amplitudes in our ganzfeld test system for a control group of 100 normal subjects between the ages of 6 and 55 years, with 6 or less diopters of myopia, were as follows: blue light, 100 to 275 μV; 0.5-Hz white light, 350 to 700 μV; and 30-Hz white flicker, 50 to 125 μV. Normal b-wave implicit times (the time interval between stimulus flash onset and the major cornea-positive peak of the rod or cone response) ranged from 71 to 108 msec for rod responses to blue light and from 25 to 32 msec for cone responses to 30-Hz white flicker.

Results

Full-field electroretinographic responses from the mother and her three daughters with microcephaly with or without chorioretinal degeneration from Family 1 are illustrated in Figure 2. In the family members affected with microcephaly and chorioretinal degeneration (Patients 1 and 3), responses to all test stimuli were reduced 60% to 70% below normal in peak-to-peak amplitude; both the cornea-negative a-wave and the cornea-positive b-wave were reduced in these patients compared with the normal a-wave and b-wave. Rod-isolated responses to blue light and cone-isolated responses to 30-Hz white flickering light were also delayed in b-wave implicit times. Cone responses were so delayed that each stimulus elicited the next plus one response (Fig. 2). Despite their difference in age, Patients 1 and 3 had similar amplitudes and implicit times to all test stimuli (Fig. 2). In contrast, the family members with microcephaly without chorioretinal degeneration (the mother in Family 1 and Patient 2) had normal amplitudes and implicit times. The normocephalic father had normal electroretinograms.

Full-field electroretinograms from the man with microcephaly and chorioretinal degeneration (Patient 4), which were recorded over a 14-year interval, are illustrated in Figure 3. Responses to dim blue light could not be reliably interpreted because of some reflex blinking. Responses were reduced 60% to 70% below normal in amplitude to 0.5-Hz white light and 20% to 30% below normal to 30-Hz white flickering light. Cone responses to 30-Hz white flickering light were minimally delayed in b-wave implicit time. No significant reductions in the electroretinograms were observed over 14 years in this patient.

Discussion

The present study shows that patients with microcephaly and chorioretinal degeneration have reduced rod and cone components in their full-field electroretinograms; the reductions in amplitude to 0.5-Hz white light were greater than 50% below normal, suggesting that the loss of photoreceptor cells exceeded the area of chorioretinal atrophy seen in the inferior fundus on ophthalmoscopic examination. Loss of amplitude in the full-field electroretinograms to 30-Hz white flickering light indicates that peripheral (that is, extramacular) cones must be involved. The presence of retinal arteriolar narrowing in all quadrants was also consistent

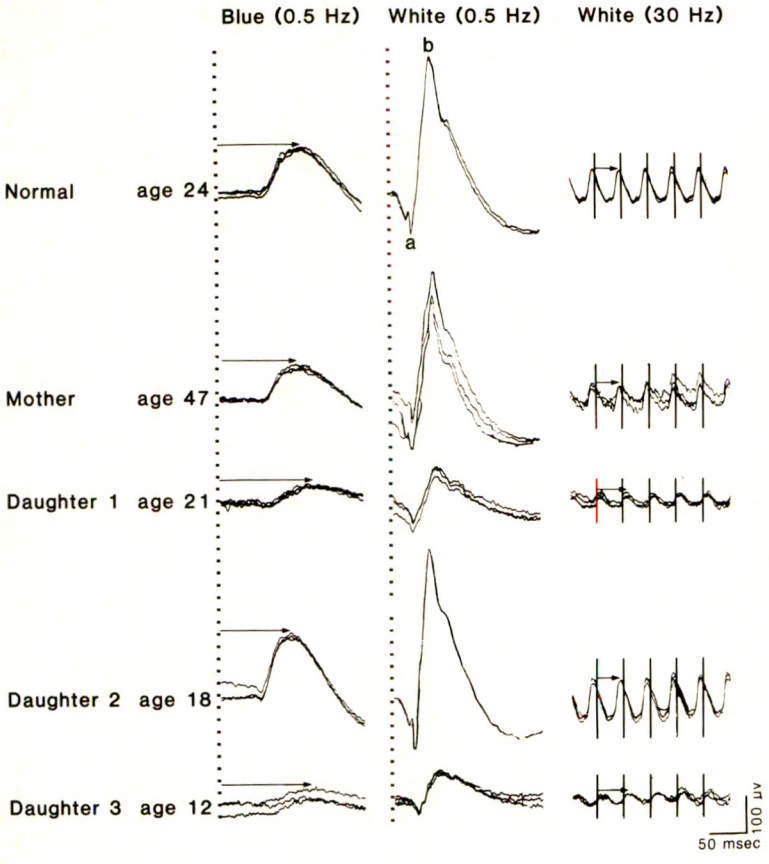

Fig. 2 (Manning, Bruce, and Berson). Full-field electroretinograms from a representative normal subject and a mother and her three daughters with microcephaly with or without chorioretinal degeneration. Stimulus onset is indicated by vertical hatched lines in columns 1 and 2 and vertical shock artifacts in column 3. Two or three consecutive responses are illustrated. Rod b-wave implicit times in column 1 and cone b-wave implicit times in column 3 are indicated by horizontal arrows.

with the idea that the retinal malfunction involved large areas of the retina. The absence of intraretinal bone spicule pigment and the delays in b-wave implicit times distinguish these patients from previously described patients with sector retinitis pigmentosa who had intraretinal bone spicule pigment and normal b-wave implicit times.[25,31]

Two female siblings from Family 1, born nine years apart, had virtually the same electroretinographic amplitudes, visual fields, and fundus appearance. Similarly, Patient 4 from Family 2, aged 23 years, who was tested with the electroretinogram initially at age 9 years, showed no change in retinal function over a 14-year interval. These findings would suggest that the retinal condition is stable, at least in young adult life. The long-term course remains to be defined, particularly because delayed cone or rod b-wave implicit times, or both, have been associated with progressive disease in other forms of hereditary retinal degeneration.[24-28]

The chorioretinal degeneration found in the patients in this study differs from the chorioretinopathy characteristics of Aicardi's syndrome. Patients with Aicardi's syndrome have myoclonic seizures, severe mental retardation, chorioretinopathy, and agenesis of the corpus callosum.[32,33] Our patients did not have myoclonic seizures, and a computed tomographic scan of Patient 1 did not show agenesis of the corpus callosum. The chorioretinal lacunae of Aicardi's syndrome are peripapillary and typically do not extend beyond the midperiphery[32,33] in contrast to the inferior chorioretinal degeneration in our patients. Additionally, electroretinograms of patients with Aicardi's syndrome have been reported to have normal b-wave amplitudes and implicit times[32] in contrast to the reduced and delayed electroretinograms in our patients.

The cause of the chorioretinal degeneration is unknown. The hypoplastic process affecting the brain can apparently affect the eyes in some patients. This is supported in the present study by the presence of microcephaly with or without chorioretinal atrophy in Family 1. Embryologically, the optic vesicle invaginates into its more proximal portion to form the optic cup, which is incomplete inferiorly at the choroidal

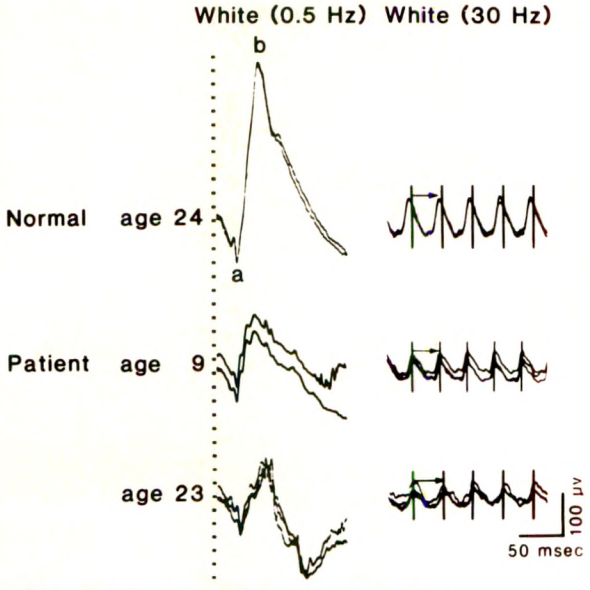

Fig. 3 (Manning, Bruce, and Berson). Full-field electroretinograms from a representative normal subject and a patient with microcephaly and chorioretinal degeneration examined at ages 9 and 23. Two or three consecutive responses are illustrated. Horizontal arrows in the right-hand column designate cone b-wave implicit times.

fissure. In time, the choroidal fissure fuses from an intermediate position proximally and distally.[34] The inferior location of the chorioretinal atrophy raises the possibility of some degree of failure of the primordial choroidal fissure to fuse, but none of our patients showed other signs of failure of closure of the fissure, such as a coloboma of the disk or iris.

In Family 1, the transmission of microcephaly with or without chorioretinal degeneration over two consecutive generations suggests that this condition is inherited in a dominant mode with variable penetrance, but an autosomal recessive mode of inheritance cannot be excluded. The genetic abnormality leading to this condition remains to be determined.

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OPHTHALMIC MINIATURE

"I never saw a cat with blazing red eyes," said Qwilleran.

"You will find that characteristic of Siamese cats. Shine a light in their eyes, and they turn ruby red. Ordinarily they are blue—like the blue in that Van Gogh. See for yourself when the cat decides to flatter us with his presence. For the moment he prefers seclusion. He is busy sensing you. Already he knows several things about you."

Lilian Jackson Braun, *The Cat Who Could Read Backwards*
New York, Jove Books, 1986, p. 57

Iris Neovascularization After Central Retinal Artery Obstruction Despite Previous Panretinal Photocoagulation for Diabetic Retinopathy

James F. Vander, M.D., Gary C. Brown, M.D., and William E. Benson, M.D.

Five consecutive patients with proliferative diabetic retinopathy who were treated successfully with panretinal photocoagulation subsequently developed a central retinal artery obstruction. Iris neovascularization developed in the affected eye within one to three months after the obstruction in four of the five patients despite the previous laser treatment. Additional retinal ischemia, as occurs in central retinal artery obstruction, appears to promote marked iris neovascularization in a large percentage of patients, even when successful photocoagulation for proliferative retinopathy has been previously administered.

NEOVASCULARIZATION of the iris occurs in association with many retinal vascular diseases and frequently leads to the development of a blind, painful eye because of neovascular glaucoma.[1] In many of these conditions, panretinal photocoagulation has been shown to cause regression of the iris neovascularization and prevention of neovascular glaucoma. Central retinal artery obstruction can lead to the development of iris neovascularization in as many as 17% of patients.[2] Recent evidence has shown that panretinal photocoagulation may be helpful in inducing regression of iris neovascularization and prevention of neovascular glaucoma in patients after central retinal artery obstruction.[3] Five consecutive patients with proliferative diabetic retinopathy who were treated with panretinal photocoagulation later experienced a central retinal artery obstruction. Marked neovascularization of the iris developed in four of the five patients. The diabetic retinopathy had been documented as being stable before the arterial obstruction in each patient.

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Case Reports

Case 1

A 78-year-old white woman with a history of diabetes mellitus for 20 years had a visual acuity of R.E.: 20/70 and L.E.: 20/200 on initial examination. An anterior chamber intraocular lens was present in the left eye. Background diabetic retinopathy was noted in both eyes. One year later, a small vitreous hemorrhage and neovascularization of the retina were noted in the right eye, and panretinal photocoagulation was performed. Using a 500-μm spot size, 2,800 burns were given with the argon green laser over four sessions. The neovascularization regressed in response to this therapy. The patient subsequently underwent cataract extraction with insertion of a posterior chamber intraocular lens in the right eye. Visual acuity improved to 20/50, which remained for 2½ years. At that time, the patient noted sudden loss of vision in the right eye. Visual acuity was R.E.: hand motions and L.E.: 20/100. A cherry-red spot with retinal whitening was present in the fundus of the right eye, and the diagnosis of acute central retinal artery obstruction was made. No retinal neovascularization was apparent. Intravenous fluorescein angiography

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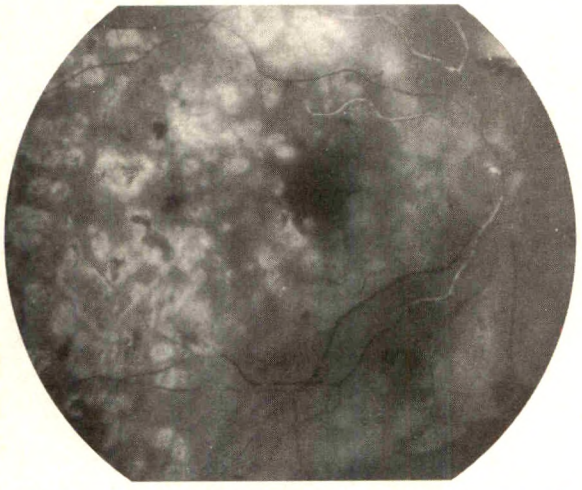

Figure (Vander, Brown, and Benson). Fluorescein angiogram at 291 seconds after injection. The study shows marked retinal vascular hypoperfusion with a normal choroidal filling pattern.

disclosed a marked delay in filling of the retinal vasculature with a normal choroidal filling pattern (Figure). The intraocular pressure was 18 mm Hg, and no neovascularization of the iris was present. One month later, the visual acuity had dropped to R.E.: light perception, and the intraocular pressure was 60 mm Hg. Marked neovascularization of the iris and angle was present. Cyclocryotherapy was performed with a reduction in the intraocular pressure to less than 20 mm Hg. The visual acuity decreased to no light perception, but the eye remained comfortable. The left eye has remained stable with only background diabetic retinopathy for one year.

Case 2

A 43-year-old black woman with an 18-year history of diabetes mellitus and systemic arterial hypertension had a visual acuity of R.E.: 20/60 and L.E.: 20/30 on initial examination. A mild vitreous hemorrhage was present in the right eye, and neovascularization of the optic disk and retina could be seen in the left eye. The patient underwent panretinal photocoagulation in both eyes. Using a 500-μm spot size, 951 burns were delivered to the right eye with the argon green laser over two sessions. Six months after the laser therapy, the patient underwent pars plana vitrectomy for nonclearing vitreous hemorrhage in the right eye. Completion of the panretinal photocoagulation with 627 burns was performed during surgery. The immediate postoperative course was uneventful with visual acuity of R.E.: 20/50 and L.E.: 20/20 at four weeks after surgery. The intraocular pressure was 18 mm Hg bilaterally. There was no iris or detectable retinal neovascularization. One month later, the patient returned because of abrupt visual loss in the right eye, which had occurred three days previously. The visual acuity had decreased to R.E.: hand motions. Retinal whitening with a cherry-red spot in the macula was present, and the diagnosis of central retinal artery obstruction was made. Electroretinography disclosed a normal A-wave amplitude and a diminished B-wave amplitude, which supported the diagnosis of acute central retinal artery obstruction without accompanying choroidal ischemia. An anterior chamber paracentesis was performed, and treatment was instituted with carbon dioxide 5%/oxygen 95% for five minutes every two hours for two days. Topical 0.5% timolol was also begun two times daily. Five weeks later, the patient returned with pain and redness of the right eye. The visual acuity had decreased to R.E.: no light perception. Marked neovascularization of the iris was present, and the intraocular pressure had increased to 43 mm Hg. Medical management of the increased intraocular pressure was begun. Two years later, the visual acuity remained R.E.: no light perception and L.E.: 20/20. No iris or retinal neovascularization was present in the left eye.

Case 3

A 49-year-old white man with an 18-year history of noninsulin dependent diabetes mellitus had 20/20 visual acuity and neovascularization of the optic nerve and retina in both eyes. The patient underwent panretinal photocoagulation in both eyes, with subsequent regression of the retinal neovascularization bilaterally. Using a 500-μm spot size, 2,017 burns with the argon green laser were delivered to the right eye over four sessions. Eight months later, abrupt loss of vision in the right eye developed. Visual acuity was R.E.: counting fingers and L.E.: 20/20. Retinal whitening with a cherry-red spot in the fovea was present in the right eye. The diagnosis was acute central retinal artery obstruction. No iris or retinal neovascularization was seen. An anterior chamber paracentesis was performed, and topical 0.5%

timolol was given two times daily. One month later, the patient returned with pain and a further decrease in vision in the right eye. The visual acuity had decreased to R.E.: hand motions. Marked neovascularization of the iris was present, as well as increased intraocular pressure to 54 mm Hg. Medical management for the neovascular glaucoma was initiated. The left eye has remained stable for 48 months.

Case 4

A 70-year-old black woman with a 15-year history of diabetes mellitus had severe retinal neovascularization in both eyes. Bilateral panretinal photocoagulation was performed. Using a 500-μm spot size, 2,009 burns of argon green laser were delivered to the left eye over three sessions. The visual acuity was R.E.: counting fingers and L.E.: 20/50 with regression of the retinal neovascularization bilaterally. Diabetic macular edema in each eye accounted for the decreased visual acuities. One year later, the patient noted sudden loss of vision in the left eye. Examination disclosed a visual acuity of L.E.: counting fingers and an acute central retinal artery obstruction with retinal whitening and a cherry-red spot in the fovea of the left eye. No neovascularization of the iris or retina was seen. Treatment included an anterior chamber paracentesis, carbonic anhydrase inhibitors, and topical 0.5% timolol. Two months later, the retinal whitening had resolved, and results of the examination were otherwise unchanged. By three months after the acute central retinal artery obstruction, the visual acuity had decreased to L.E.: hand motions, and marked neovascularization of the iris was present. The intraocular pressure, previously normal, had risen to 65 mm Hg. Cyclocryotherapy was performed for pain control. The retinopathy in the right eye has remained inactive for 24 months.

Case 5

A 42-year-old white man with a 20-year history of diabetes mellitus had sudden marked visual loss in the right eye three days before initial examination. Previously, the patient could read small print easily. Vision in the left eye was lost many years before because of rhegmatogenous retinal detachment. Two years before initial examination, panretinal photocoagulation for proliferative diabetic retinopathy had been performed elsewhere in the right eye. The laser burn size and number of burns created are not known. On examination, visual acuity was R.E.: counting fingers at four feet and L.E.: no light perception. Diffuse retinal whitening with a cherry-red spot was present in the right eye. Heavy panretinal photocoagulation scars were present. There was no retinal or iris neovascularization. The diagnosis was acute central retinal artery obstruction. The left eye was phthisical. Fluorescein angiography disclosed a marked delay in retinal arterial filling with some cilioretinal sparing of the papillomacular bundle. The choroidal filling pattern was normal. Treatment consisted of topical 0.5% timolol, oral acetazolamide, anterior chamber paracentesis, and 5% carbon dioxide/95% oxygen. Results of diagnostic evaluation, including digital subtraction carotid angiography, were normal. Monthly follow-up examinations showed no significant changes except for a modest improvement in visual acuity to R.E.: 20/400 five months after the central retinal artery obstruction. Three months later, the visual acuity had improved to 20/50. Three years later visual acuity was 20/40. No retinal or iris neovascularization developed at any point after the arterial obstruction.

Discussion

Each of the patients described had proliferative diabetic retinopathy that had regressed after panretinal photocoagulation. The subsequent central retinal artery obstruction, however, led to the dramatic formation of iris neovascularization and severe secondary glaucoma in four of the five patients. The clinical appearance was highly suggestive of neovascular glaucoma in all patients although gonioscopic confirmation was available in only one patient. In three of the patients, the onset of neovascularization occurred within one month after the arterial obstruction, whereas in the fourth patient it developed by three months after the occlusive event.

The pathophysiologic characteristics of neovascularization of the retina and iris, and the mechanism by which panretinal photocoagulation induces regression of the neovascularization, remain uncertain. Traditionally, investigators have hypothesized that widespread retinal ischemia, as occurs in diabetic patients,

results in the production of an angiogenic factor capable of inducing neovascularization. Laser treatment presumably destroys the retinal cells responsible for the production of this factor, and regression of the new vessels results.

Newer evidence suggests that the development of neovascularization is more complicated. An alteration of the relative balance of a group of extracellular modulating factors secreted by the retina and adjacent tissues has been suggested as the principle mechanism for the development and regression of neovascularization.[4] Glaser[4] has shown that certain peptides may function as both inhibitors and promoters of neovascularization and hypothesized that their actual function depends on a number of extracellular modulating factors. The nature of many of these factors remains uncertain.

The mechanism of the response of neovascularization to photocoagulation is also controversial. Possibly, the retinal cells that produce an angiogenic factor are destroyed.[5] Weiter and Zuckerman[6] suggested that photocoagulation of the photoreceptors and retinal pigment epithelium removes the high-oxygen consuming complex of the retina and allows choroidal oxygen to diffuse into the inner retina, thus removing the hypothesized hypoxic stimulus for neovascularization. Production of an angiogenesis inhibitor or alterations in the balance of extracellular modulating factors are other possible mechanisms of the photocoagulation effect.[7]

Although not every patient with proliferative diabetic retinopathy will respond completely to panretinal photocoagulation, those eyes that do show complete regression of retinal and iris neovascularization often remain stable for many years.[8] The absence of active retinal proliferative disease and the close temporal relationship between the arterial obstructions and the onset of iris neovascularization in our patients make it unlikely that diabetic retinopathy alone accounted for the dramatic alteration in their clinical courses. Furthermore, the absence of the typical clinical, fluorescein angiographic, and electroretinographic features of the ocular ischemic syndrome[9] in our patients suggests that concomitant carotid artery obstruction or chronic ophthalmic artery obstruction were not contributing factors. More likely, the additional ischemic insult of a central retinal artery obstruction appears to have altered an otherwise stable condition. Only 13% of the retinal area is treated during standard panretinal photocoagulation, which leaves most of the retinal tissue available to respond to an insult from a central retinal artery obstruction.[10]

The incidence of iris neovascularization after central retinal artery obstruction has traditionally been thought to be small.[11,12] A recent study from our institution, however, that involved patients without proliferative diabetic retinopathy suggests that it may be as high as 17%.[2] Patients with marked retinal perfusion abnormalities on fluorescein angiography seem to be at higher risk for developing iris neovascularization. Furthermore, panretinal photocoagulation may be effective in reversing iris neovascularization and preventing neovascular glaucoma if performed before anterior chamber angle closure.[3] This study, unlike the study presented herein, also involved patients with no history of proliferative retinopathy.

Our study demonstrates that the small group of patients who have already undergone scatter panretinal photocoagulation for proliferative diabetic retinopathy and later experience an acute central retinal artery obstruction appear to be prone to the development of iris neovascularization. This does not imply that the previous photocoagulation caused the formation of the iris neovascularization, but simply that standard panretinal photocoagulation does not seem to be protective. Persons with the features described herein should be followed up carefully for the first three months after the central retinal artery obstruction because of the possibility that severe glaucoma may ensue.

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OPHTHALMIC MINIATURE

Now I shift my gaze. What I see is not the machines, but Ofglen, reflected in the glass of the window. She's looking straight at me.

We can see into each other's eyes. This is the first time I've ever seen Ofglen's eyes, directly, steadily, not aslant. Her face is oval, pink, plump but not fat, her eyes roundish.

Margaret Atwood, *The Handmaid's Tale*
Boston, Houghton Mifflin Company, 1986, p. 167

Clinical and Histologic Effects of Extreme Intraocular Hypothermia

John D. Zilis, M.D., David Chandler, B.S., and Robert Machemer, M.D.

Rabbit eyes in which vitrectomy was performed underwent three hours of hypothermic perfusion with either 22 C or 2 C lactated Ringer's solution. Clinical, electroretinographic, fluorescein angiographic, histologic, and ultrastructural examinations were performed. No changes were noted in eyes cooled with 22 C fluid. Reversible lens opacities, equivocal electroretinographic changes, and subclinical retinal detachments were found in the eyes cooled with 2 C fluid. Extreme cooling of eyes is not advisable, although temperatures of 22 C are well tolerated.

Cooling a biologic system slows metabolic activity. Mild intraocular cooling to 22 C has been shown to be effective in protecting the retina from light damage.[1] Others[2,3] have assessed the effect of more profound hypothermia on bleeding, postoperative inflammation, and the electroretinogram. This study was designed to assess the possible limitations of extreme intraocular hypothermia in the rabbit eye.

Material and Methods

We used 20 Dutch belted rabbits that weighed 2 to 3 kg. At least two weeks before vitreous surgery, the rabbits were anesthetized with an intramuscular injection of 100 mg of ketamine and 10 mg of xylazine. Pupils were dilated by using a 1:1 mixture of 0.25% tropicamide and 5% phenylephrine. Peripheral retinal cryopexy was placed 4.0 mm behind the corneoscleral limbus for 360 degrees, under direct visual observation, in preparation for future sclerotomy sites.

One to two days before surgery, the animal was again anesthetized, and both pupils were dilated for electroretinography. Using a Cadwell 5200 system with a Grass photostimulator, a ganzfeld electroretinogram was recorded from both eyes simultaneously. The b-wave amplitude of each eye was measured, and the findings were expressed as a ratio by dividing the study eye b-wave amplitude by the fellow control eye b-wave amplitude.

A preoperative clinical examination including fundus photography was performed, and a fluorescein angiogram was obtained after the injection of 0.2 to 0.3 ml of a 10% sodium fluorescein solution into an ear vein.

On the day of surgery, the rabbit was anesthetized, and the pupil of the experimental eye was dilated. Supplemental anesthesia was given approximately every 40 to 60 minutes as required. A retrobulbar injection was not given. Rectal temperature was monitored, and a heat lamp was used to maintain stable body temperature as needed. The cornea remained covered except when retinal visualization was required.

Three sclerotomies were created 3.0 mm posterior to the corneoscleral limbus, and cannulas[4] were placed and secured with preplaced sutures. Before intraocular infusion was begun, the temperature in the midvitreous was measured by using a thermocoupled, 24-gauge hypodermic probe and telethermometer, which was calibrated to within a 0.1 C error.

A vitrectomy was performed using Ringer's lactate solution at either 22 C or 2 C. Room temperature (22 C) fluid was obtained by placing the 1-liter bags in the operating room for several days before surgery. Cold (2 C) fluid was prepared on the day before surgery by placing the bags in an elevated refrigerator. The infusion line was surrounded with insulation

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From the Devers Eye Institute, Portland, Oregon (Dr. Zilis) and Duke University Eye Center, Durham, North Carolina (Mr. Chandler and Dr. Machemer). This study was presented in part at the Association for Research in Vision and Ophthalmology Meeting, New York, May 2, 1989. This study was supported by National Institutes of Health-National Eye Institute grant 1 F32 EY06046-01, the Helena Rubinstein Foundation, New York, and Research to Prevent Blindness, Inc., New York.

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tubing to minimize heat exchange. All infusion bags were elevated 26 inches above the level of the cornea to maintain a steady infusion flow rate and stable intraocular temperature. Using this high-flow, open cannula system, the measured intraocular pressure was 6.0 to 11.0 mm Hg.

Vitreous was removed centrally and near the areas of the sclerotomies to assure adequate and constant infusion flow. The thermometer was advanced into the vitreous cavity to within 2.0 mm of the retina by using a micromanipulator. The duration of infusion was three hours. The preretinal temperature was continuously monitored. The mean preretinal temperature in the ten rabbits of the 22 C group was 23 ± 0.48 C and 6.49 ± 0.61 C in the 2 C group.

Flow rate was measured by counting the number of drops per minute in the drip chamber of the infusion set during the experiment. The number of drops per milliliter was then determined for each individual infusion set at the end of the procedure. The mean infusion flow rate was 13.8 ml/min in the 22 C group and 13.4 ml/min in the 2 C group.

After the three-hour perfusion, the sclerotomies were closed with 7-0 Vicryl. Gentamicin (5 mg) was injected beneath the conjunctiva, and dexamethasone-neomycin-polymyxin and atropine 1% ointment were placed topically on the eye.

Animals were examined on postoperative days 1, 3, 6, and 7. Color photography was performed on day 1 or, if media were hazy, on day 3 and was repeated with fluorescein angiography on day 6. The electroretinogram was repeated on day 7 under anesthesia.

One animal from each group (22 C or 2 C) of ten rabbits was killed on the first postoperative day, and the remaining nine rabbits in each group were maintained for seven days after surgery. Both the experimental and the nonoperated on fellow eyes were enucleated with immediate injection of 3% glutaraldehyde in 0.1 M cacodylate buffer into the vitreous cavity followed by refrigeration for 24 hours.

A posterior eye cup was prepared, and rectangular blocks of tissue from the temporal vascular wing and the avascular visual streak below the optic disk were taken. The specimens were placed in 2% osmium tetroxide and processed and embedded in epoxy resin. Sections were stained with methylene blue and azure II for light microscopy. Thin sections were stained with uranyl acetate and lead citrate for transmission electron microscopy. A peripheral strip of tissue from the superior ora serrata through the vascular wing to the inferior ora serrata was also removed for paraffin embedding.

Results

No intraoperative or postoperative lens changes were noted in the animals treated with 22 C infusion. Two eyes subjected to the cold (2 C) infusion developed lens changes after 120 minutes of infusion. Somewhat abruptly, the sutural lines of the lens became prominent followed by a ground glass clouding of the posterior lens. The lens opacities remained for several hours after surgery, but clarity returned within the first 24 hours postoperatively.

Mild bleeding from the sclerotomy sites at closure was noted in two eyes from the 22 C group and in three eyes from the 2 C group.

Postoperative inflammation was assessed as mild haze (1+), haze that interfered with photography (2+), haze that obscured vessel detail (3+), and no retinal detail visible (4+). Seven of ten animals in each group showed a postoperative inflammatory response. The only difference in the two groups was seen on the first postoperative day with the 22 C group showing a mean 2+ response compared to a 2.5+ response in the 2 C group. Progressive clearing was seen in both groups over the ensuing week.

Retinal detachment or edema was not apparent in either group postoperatively. Fluorescein angiography failed to show leakage from retinal vessels or the retina at day 6.

Electroretinographic comparison of the preoperative and postoperative b-wave ratios is shown in Figure 1. All nine eyes treated with 22 C infusion evaluated at one week displayed at least an 85% return to the preoperative baseline. The 2 C group showed greater variability postoperatively, and two eyes failed to achieve more than 75% of the preoperative level.

The eyes of the two animals (one from each group) that were enucleated 24 hours after surgery were histologically assessed. No significant changes were seen. Both experimental eyes had an artifactually detached retina. The avascular and vascular retinas of the 18 nonoperated on eyes, which served as controls, and the nine eyes of the 22 C group enucleated one week after surgery, showed no apparent damage to the retina, pigment epithelium, or cho-

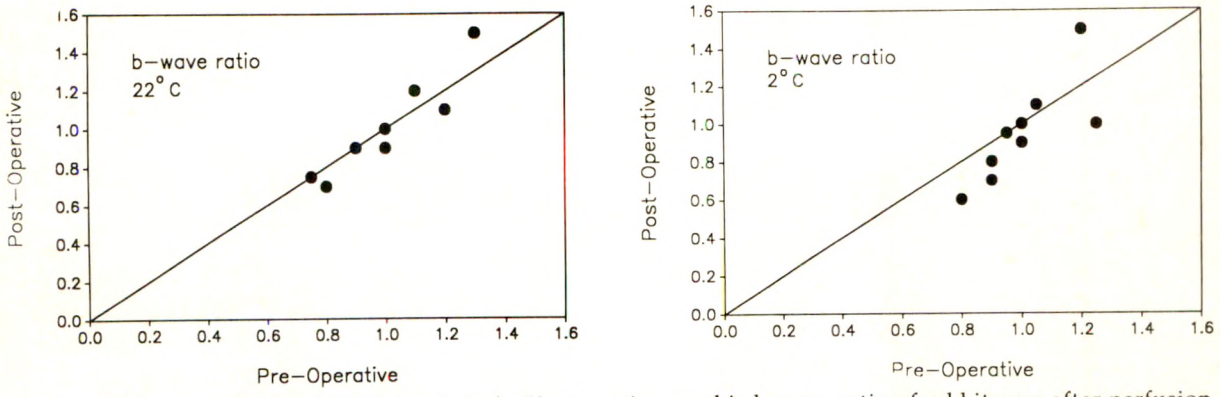

Fig. 1 (Zilis, Chandler, and Machemer). Left, Electroretinographic b-wave ratio of rabbit eyes after perfusion with 22 C infusion fluid. Comparison of preoperative and postoperative b-wave ratios between operated and unoperated on eyes. Right, Electroretinographic b-wave ratio of rabbit eyes after perfusion with 2 C infusion fluid. Comparison of preoperative and postoperative b-wave ratios between operated and unoperated on eyes.

roid on examination with light or transmission electron microscopy (Fig. 2).

Seven of the nine eyes in the 2 C group had obvious outer retinal and pigment epithelial damage. Loss and disorganization of photoreceptors with macrophage infiltration was seen in seven eyes (Figs. 3 and 4). This was accompanied, at times, by serous fluid accumulation (Fig. 4). Areas of damage often appeared patchy. Under the vascular wing, a low-lying detachment with severe loss of photoreceptor cells was found in two eyes (Fig. 5). The retinal pigment epithelial layer appeared flattened with proliferation of the retinal pigment epithelium in some areas.

Discussion

The potential benefits of intraocular hypothermia[1,2,5] have been recently demonstrated, and it has been proposed that more extreme cooling might be even more desirable for enhanced protection from general surgical trauma and light damage. Yet, little is known about the potential damage from cooling the eye. Transient lens changes have been described with extreme levels of cooling,[2,6] and a reversible reduction in the electroretinogram has been shown during acute cooling.[3,7]

We discovered no lens changes in the 22 C

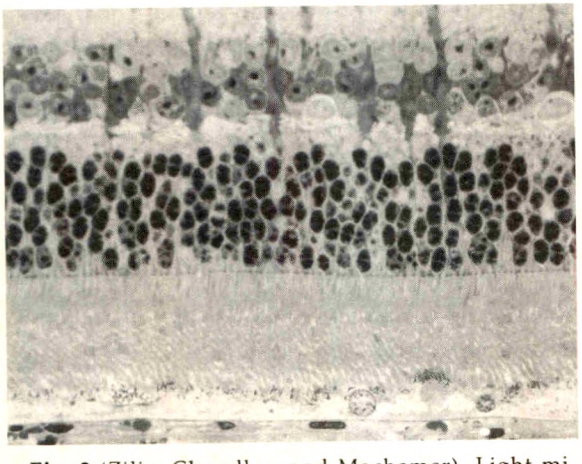

Fig. 2 (Zilis, Chandler, and Machemer). Light micrograph of rabbit retina after 22 C perfusion with Ringer's solution seven days postoperatively. No damage is apparent.

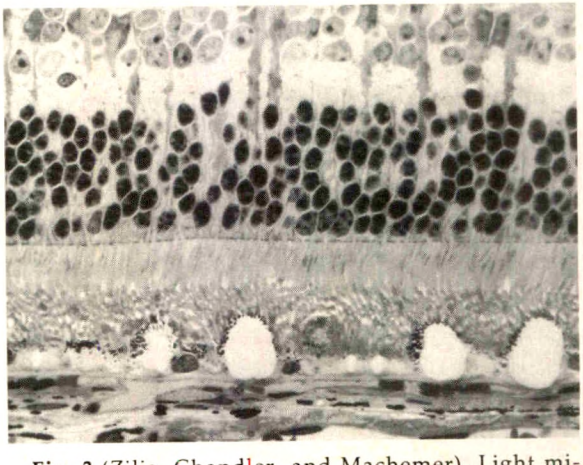

Fig. 3 (Zilis, Chandler, and Machemer). Light micrograph of rabbit retina after a 2 C perfusion with Ringer's solution seven days postoperatively. Photoreceptor disorder with macrophage infiltration.

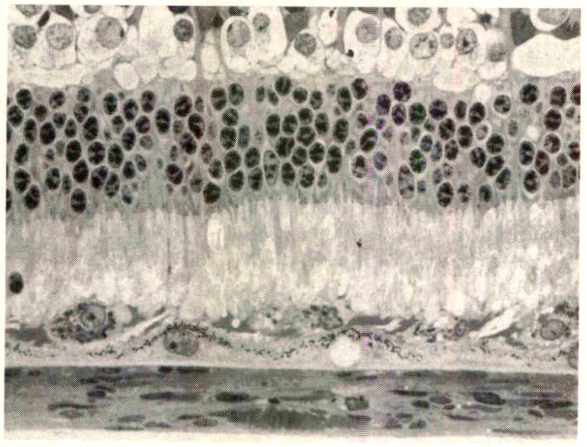

Fig. 4 (Zilis, Chandler, and Machemer). Light micrograph of rabbit retina after a 2 C perfusion with Ringer's solution seven days postoperatively. Photoreceptor damage, macrophage infiltration, and subretinal serous fluid accumulation.

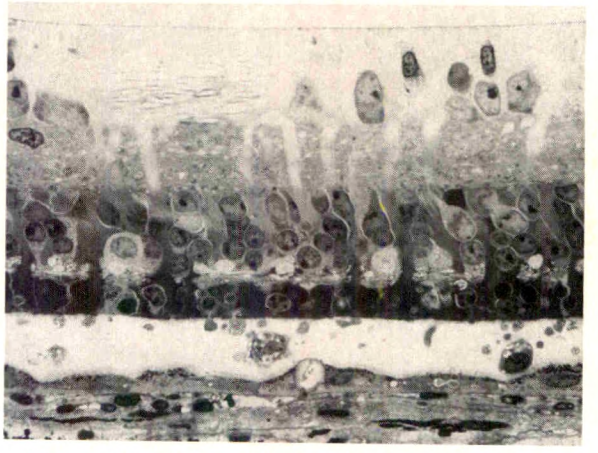

Fig. 5 (Zilis, Chandler, and Machemer). Light micrograph of rabbit retina after a 2 C perfusion with Ringer's solution seven days postoperatively. Serous retinal detachment with severe loss of photoreceptors, macrophage invasion of subretinal space, and retinal pigment epithelial changes.

infusion eyes and only a few clinical, visible changes were seen with extreme cooling. After 120 minutes of 2 C infusion, the lenses of two eyes did undergo abrupt change over several minutes. Initially, the lens sutural lines became prominent followed by a diffuse, ground glass clouding of the posterior lens. The lenses regained clarity, however, during the first postoperative 24 hours.

Postoperative inflammation is common in the rabbit eye after any intraocular procedure. Thus, we were not surprised to find inflammation in both groups with equal frequency (seven eyes, 70%) and similar severity during the early postoperative period. Progressive resolution was noted in all eyes over the ensuing postoperative week.

Fluorescein angiography disclosed no abnormalities on the sixth postoperative day in all animals of both groups. Because of hazy media and diffuse leakage often seen in the early postoperative period, we avoided performing angiography before the sixth day. Finally, the electroretinogram recorded at day 7 exhibited no striking changes when the b-wave ratio between the operated and unoperated on eye was compared to the preoperative electroretinographic values. Two rabbits in the 2 C group, however, regained only 75% of their preoperative electroretinographic value. Both of these animals showed severe histologic changes.

All eyes in the 22 C group appeared normal histologically. With so few apparent clinical changes, the histologic damage encountered in the 2 C eyes was unexpected. Seven of nine eyes in the 2 C group enucleated at seven days displayed significant outer retinal and retinal pigment epithelial damage. Possibly, the retinal damage, especially in the outer retina, is secondary to the retinal pigment epithelial damage. We have seen similar outer retinal necrosis after subretinal blood injection.[8] The accumulation of serous fluid suggests damage to the postulated retinal pigment epithelial pump.[9] The time course of the injury remains obscure because we examined only one eye from each group at 24 hours after perfusion. These eyes showed no retinal damage.

The clinical assessment underestimated the histologic damage encountered in the 2 C eyes. Most of our clinical measurements could be performed reliably only after several postoperative days. By then, the acute damage may have subsided. In the early period, intraocular inflammation limited visualization of fine retinal detail and may have obscured retinal damage. The electroretinogram in the immediate postvitrectomy period is often depressed,[10] and therefore was not used immediately after surgery in this study. Although the two eyes with the greatest postoperative decline in the b-wave ratio were found to have marked retinal damage, the electroretinogram in general poorly reflected the histologic damage encountered. The electroretinogram, which measures mass retinal response,[11] might not be sensitive

enough to focal, patchy damage, which was most prominent under the vascular medullary wings. In the rabbit, this region of the retina is morphologically attenuated, and its functional potential has been questioned.[12]

The results of this study suggest that mild intraocular hypothermia (22 C) appears to be safe, whereas extreme cooling is not advised. Because hypothermia has been shown to protect the retina from light damage, the use of moderately cooled infusion fluids during vitreous surgery may be appropriate.

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Estrogen and Progesterone Receptors and Human Conjunctiva

Lawrence A. Gans, M.D., Steven F. Lee, M.D., Michael A. Lemp, M.D., and Jay S. Pepose, M.D.

Freshly frozen conjunctival tissue from premenopausal and postmenopausal women and male subjects were processed for estrogen and progesterone receptors by using monoclonal antibodies and a peroxidase-antiperoxidase technique. No immunocytochemical staining was localized in the nuclei of the cells treated with the monoclonal antibodies to human estrogen receptor or human progesterone receptor in any of the conjunctival specimens, in contrast to the strongly positive staining in breast adenocarcinoma controls. Immunocytochemical staining disclosed no evidence for estrogen or progesterone receptors on cells of the ocular surface.

SOME EVIDENCE SUGGESTS that lacrimal gland and ocular surface tissues may be hormone sensitive.[1-5] Prompted by the prevalence of keratoconjunctivitis sicca in postmenopausal women, Potter and associates[1] sought and found cyclical variations in conjunctival epithelial maturation paralleling the menstrual cycle in premenopausal women. Sullivan and Allansmith[2] reported the modulation of IgA levels by androgens in tears of rats. Histologic changes in lacrimal gland tissue and conjunctiva in rabbits after oophorectomy were demonstrated by Jacobs and associates.[3] Kramer and associates[4] reported histopathologic changes and deficiency in ocular mucus glycoprotein in rabbits tested with the nonsteroidal antiestrogen drug, tamoxifen. Prolactin immunoreactivity in and around human lacrimal secretory cells was demonstrated by Frey and associates.[5] During pregnancy or when started on a regimen of oral contraceptives containing combinations of estrogen and progesterone, some women experience contact lens intolerance, which may be attributable to changes in corneal curvature or tear production. Prompted by these cumulative findings, we processed conjunctival tissue from premenopausal and postmenopausal women and from male subjects for estrogen and progesterone receptors by using monoclonal antibodies and a peroxidase-antiperoxidase technique.

Material and Methods

Conjunctival biopsy specimens were mounted in optimum cutting temperature compound (Miles Inc., Elkhart, Ind.), immediately snap-frozen by rapid immersion into liquid nitrogen, and stored at −80 C. The frozen tissue was transversely hemisectioned at 8-μm intervals with a cryostat. Frozen sections were placed on slides treated with tissue adhesive (Abbott Laboratories, North Chicago, Ill.). The slides were then placed in 3.7% formaldehyde–phosphate-buffered saline solution for 15 minutes. The slides were then transferred to a phosphate-buffered saline bath for five minutes, then to a methanol bath at −20 C for five minutes, and then to an acetone bath at −20 C for three minutes. The specimens were then washed in phosphate-buffered saline and stored at −20 C in a 6.9 mM MgCl, 50% glycerol, and 8.56% sucrose solution.

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From the Departments of Ophthalmology and Visual Sciences (Drs. Gans, Lee, and Pepose) and Pathology (Dr. Pepose), Washington University School of Medicine, St. Louis, Missouri, and the Center for Sight (Dr. Lemp), Georgetown University Medical Center, Washington, D.C. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc. Dr. Lee is the recipient of a National Institutes of Health Vision Science Training Grant (EY07057). Dr. Pepose is the recipient of the American College of Surgeons Faculty Fellowship (1989–1990).

Reprint requests to Jay S. Pepose, M.D., Department of Ophthalmology, Box 8096, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110.

All immunocytochemical reagents, except the anti-PgR monoclonal antibody, were provided in the Abbott ER-ICA Monoclonal kit (Abbott Laboratories, North Chicago, Ill.), which has been described previously.[6-9] Fixed specimens at −20 C were placed in a phosphate-buffered saline bath for five minutes at room temperature. Goat serum was then added to the specimen for 15 minutes. After removing the goat serum, the slides were incubated with a rat monoclonal antibody to human estrogen receptor for 30 minutes at room temperature. After being washed in phosphate-buffered saline, the slides were incubated with goat anti-rat immunoglobulin for 30 minutes. After another wash step, slides were incubated with a peroxidase-antiperoxidase complex for 30 minutes. Slides were then washed and developed with a diaminobenzidine and hydrogen peroxide solution for six minutes. After counterstaining with hematoxylin, the slides were examined with a light microscope. A positive reaction product was indicated by a red-brown immunocytochemical stain localized in the nuclei of cells.

Results

The positive control slides of human breast adenocarcinoma, pleural effusion MCF7 cell line[10] (Abbott Laboratories), contained estrogen receptor–positive cells. The immunocytochemical staining for estrogen receptor or progesterone receptor was localized exclusively in the nuclei of control cells treated with the monoclonal antibody to human estrogen receptor (Fig. 1) or progesterone receptors, respectively. The nuclei of control cells treated with a negative control antibody had no reaction product (Fig. 2).

Conjunctival biopsy specimens from the following three groups were tested: premenopausal women (21, 24, 25, and 36 years of age), postmenopausal women (51, 56, and 66 years of age), and men (23, 24, 25, and 43 years of age). No immunocytochemical staining was localized in the nuclei of the cells treated with the monoclonal antibody to human estrogen receptor or human progesterone receptor in any of the specimens (Fig. 3). Similar findings were obtained in processing three corneal specimens from premenopausal women with keratoconus.

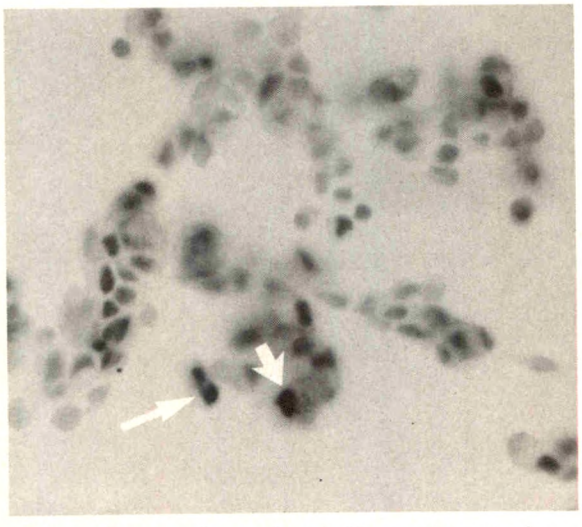

Fig. 1 (Gans and associates). Human breast adenocarcinoma cell controls show distinct nuclear staining (arrows) with a monoclonal antibody to human estrogen receptor and the peroxidase-antiperoxidase technique.

Discussion

The preponderance of tear-film deficiency syndromes in postmenopausal women is well established, yet hormonal replacement therapy has not been shown to alter objective tests of tear function. Indeed, the suggestion that women taking oral contraceptives containing estrogen and progesterone have decreased tear production was not supported in a prospective

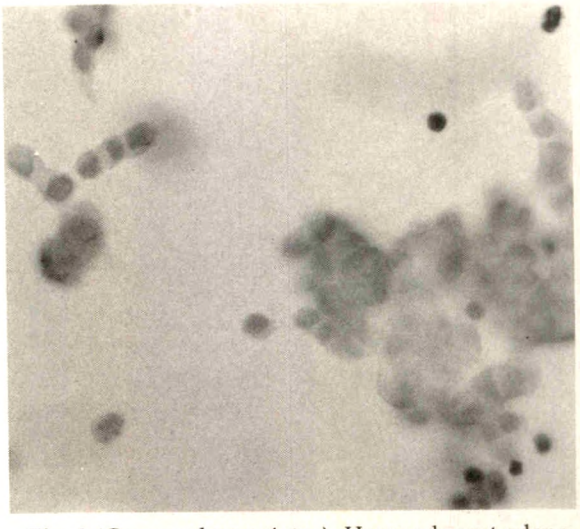

Fig. 2 (Gans and associates). Human breast adenocarcinoma cells show no reaction product with the negative control antibody.

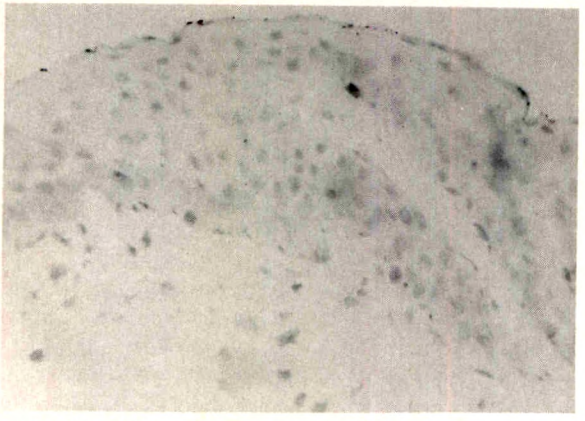

Fig. 3 (Gans and associates). Human conjunctival biopsy specimen from a premenopausal woman processed with monoclonal antibody to human estrogen receptor elicits no staining.

study.[11] The parallel variations in conjunctival epithelial maturation with the menstrual cycle found by Potter and associates[1] indicated more strongly that human ocular surface cells may be steroid responsive. In our study, immunocytochemical staining demonstrated no receptors to estrogen and progesterone in premenopausal and postmenopausal female and male conjunctiva.

Other investigators have used a variety of methods to identify various tissues expressing steroid receptors, including methods based on labeled receptor ligands for the identification and localization of estrogen receptors (sucrose-density gradient, dextran-coated charcoal, gel electrophoresis, and hydroxylapatite and gel filtration assays).[12] It was the development of highly specific monoclonal antibodies to human estrogen and progesterone receptors, however, that provided a means of detecting and studying steroid-receptor localization, structure, and function in a wide range of tissues.[13-16] Using immunocytochemical staining, estrogen receptors have been localized to the nuclei of target tissues including rabbit uterus, oviduct, corpus luteum, mammary gland, pituitary and liver, and human endometrium, breast cancer, and tissue-cultured human breast cancer cells.

The results of a more sensitive nuclear binding assay that identifies steroid receptors and measures their biologic activity[17,18] has been used to explain the existence of steroid receptors in tissues that fail to respond to physiologic or pharmacologic levels of steroid. Identification of tissues that express nonfunctional receptors may be useful in predicting response to hormone therapy.

Based on the association of estrogen deficiency and postmenopausal bone loss, the localization of estrogen receptors in skeletal tissue was attempted by the methods noted above without success until Eriksen and associates[19] demonstrated estrogen receptors' presence in normal human osteoblastlike cells. They used RNA blot analyses to measure receptor messenger RNA for the human estrogen receptor in a population of cultured human bone cells. Application of this sensitive technique may be useful in future efforts to detect and localize estrogen and progesterone receptors in cells of the ocular surface.

ACKNOWLEDGMENT

The anti-PgR monoclonal antibodies were provided by Abbott Laboratories (Diagnostic Division, Abbott Park, Ill.), and by Geoffrey Greene, M.D., Ben May Laboratories for Cancer Research, University of Chicago, Chicago, Illinois.

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EDITORIAL

What is the Evidence and Medical Advertising

Frank W. Newell

Ajax Carlson, Ph.D., was a legendary physiologist, a president of the American Physiological Society, a teacher of a generation of researchers, and longtime head of the physiology department at the University of Chicago. Although he emigrated from Sweden to Montana at an early age he never lost his accent. He was feared in class and at meetings for a question for which he demanded a precise answer, "Wot is the evidence?"

My recall of Carlson was triggered by the first advertisements for a new luxury car, which pictured beautiful landscapes and no specific information about the automobile. In the language of the creative artist the advertisements were designed to create a mood. In some respects those advertisements are similar to medical advertisements that extoll many products from lasers, intraocular lenses, and contact lenses, to advances designed to ease the life of the physician and brighten the life of the patient. Rarely is Carlson's question answered, "Wot is the evidence?"

The evidence of course is the number in the group that was tested, operated on, treated or otherwise observed together with the number of controls. The results must be provided in actual numbers and not in percentages. In respected professional publications one is provided with means, standard deviations, exact P values, and sometimes confidence intervals. Far more persuasive than the picture of a contented oldster fresh from the tennis courts with the implication that well-being arose from the use of a revolutionary new gizmo would be even a small line that N individuals had used the product and YY or whatever were able to use it successfully for NN consecutive days. Instead educated, critical professionals are apparently expected to be lulled by Zen-like surroundings

into prescribing the product for their patients without knowing any details other than its availability.

A recent letter from a practitioner extolling the use of a new contact lens gave detailed instructions for managing the first days of patient disappointment with poor vision and other problems with a promise of better days to come. Nowhere did the physician indicate how many patients had been given the lens and how many persisted to final satisfaction.

Many products do not require such evidence, and indeed with many foods, drinks, and even automobiles it is not possible. With pharmaceuticals the physician knows their action and what level of satisfaction is the goal with an individual patient. This is not true with many other products used by the physician. Rather than amorphous scenes one wishes for specific information and the answer to Carlson's question, "Wot is the evidence?"

LETTERS TO THE JOURNAL

Fatigue-Induced Familial Anisocoria

Mabel M. P. Cheng, M.D., and Robert A. Catalano, M.D.

Department of Ophthalmology, Lions Eye Institute, Albany Medical College. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

Inquiries to Robert A. Catalano, M.D., Department of Ophthalmology, Albany Medical College, Albany, NY 12208.

A 36-year-old man and his 7-year-old daughter had uniocular, fatigue-induced mydriasis of the left pupil. The father dated the onset of his disorder to childhood, and the disorder had been noted in his daughter for at least two years. Anisocoria consistently developed in both patients after about 17 hours of wakefulness and resolved after about two hours of sleep (Figs. 1 and 2). During periods of anisocoria, pupillary responses in both eyes remained brisk. There was no segmental iris palsy and reflex dilation of both irides after a bright light flash was symmetric. The anisocoria was not accentuated in light or dark illumination. There was no associated facial flushing, hyperhidrosis, conjunctival injection, blepharoptosis, blurred vision, headache, ocular pain, diplopia, or neurologic deficit. Neither patient had a history of seizures, drug or alcohol ingestion, previous ocular disorder, or head trauma. The father had a history of migraine headaches.

The absence of associated findings in our patients suggests against episodic mydriasis associated with seizures, cyclic oculomotor paresis, congenital vascular malformations, or degeneration of the cervical spine. Additionally, our patients probably do not have a migraine variant. The internal ophthalmoplegia that is occasionally seen in patients with ophthalmo-

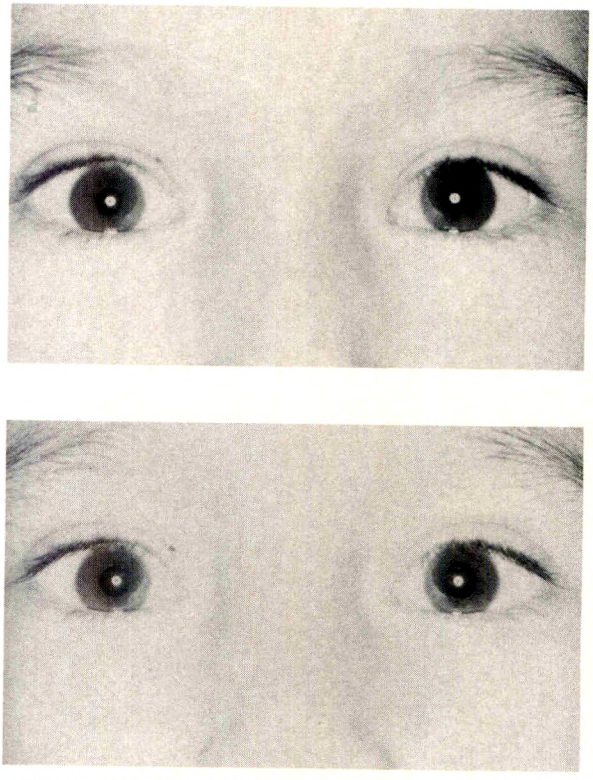

Fig. 1 (Cheng and Catalano). Pupil size in 7-year-old daughter. Top, Symmetric size during periods when not fatigued. Bottom, Mydriasis of left pupil after 17 hours of wakefulness.

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Fig. 2 (Cheng and Catalano). Pupil size in 36-year-old father. Top, Symmetric size during periods when not fatigued. Bottom, Mydriasis of left pupil after 17 hours of wakefulness.

plegic migraine typically follows or accompanies ocular or periocular pain. Furthermore, in patients with migraine the paralysis usually lasts longer than two hours and tends to persist for longer periods after repeated attacks.[1]

Our patients also cannot be categorized as having simple, central (benign) anisocoria. Although this condition is often familial, benign anisocoria decreases in light, and the mydriatic pupil typically shifts from side to side.[2]

Finally, our patients do not fit the syndrome of transient unilateral pupillary dilatation without signs of systemic or neurologic disorder. This usually has been reported in young adult women and typically is associated with blurred vision and headaches.[3] Thompson, Zackon, and Czarnecki[4] reported a subcategory of 26 similar patients without accompanying headache. Unlike our patients, the affected pupils in these patients peaked in one direction, episodes lasted only about one minute, and in no patients was the disorder associated with fatigue.

Fatigue can affect pupillary lability.[5] Perhaps in our patients fatigue accentuates an inherent asymmetry in their supranuclear control of pupillary tone. A supranuclear cause is further suggested by intact sympathetic and parasympathetic pathways and the paucity of associated autonomic findings during periods of anisocoria.

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The Effect of Light Intensity on Measurement of the Relative Afferent Pupillary Defect

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To study the effect of light intensity on measurement of the afferent pupillary defect, five patients with relative afferent pupillary defects were examined after informed consent had been obtained. Four patients had compressive optic neuropathy and one patient had a central retinal artery occlusion with sparing of the cilioretinal artery. The patients were examined in the same darkened room. They maintained fixation on a distant target during the test. The light source was a halogen indirect ophthalmoscope. A ruled tape was attached to ensure a constant distance from the subject's eyes to the

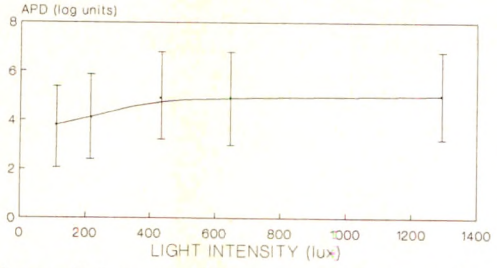

Figure (Johnson). The pooled data from five patients showing an asymptotic relationship between the measured relative afferent pupillary defect and light stimulus intensity (±S.D.). The afferent pupillary defect increases as light intensity is increased, until a steady-state level is attained beginning at 430-lux illumination.

light source. Five light stimuli (108, 215, 430, 646, and 1291 lux) were directed tangentially to the optical axis of the eyes. The light intensity was calibrated throughout the test and the order of light intensity presentations was randomized by an assistant. The examiner, who was unaware of the specific light intensity, neutralized the afferent pupillary defect with neutral density filters within three to five swings of the light source.[1] After each neutralization, both eyes were closed for three to four minutes to allow for recovery of retinal adaptation.

The pooled data (Figure) showed an asymptotic response with increasing afferent pupillary defect as light intensity increased, reaching a steady-state level beginning at 430 lux illumination. The afferent pupillary defects at steady-state level were greater than the lower (108 and 215 lux) illuminations ($P = .025$, paired Student's t-test). This result may reflect in part the retinal neuronal response to increasing light intensity that is asymptotic when fitted with the Michaelis-Menton equation.[2] As the level of illumination is increased, more retinal ganglion cells are stimulated. The maximal asymmetry of retinal ganglion cell function between the two eyes, hence the maximal relative afferent pupillary defect, occurs when most of the retinal ganglion cells are stimulated at steady state. One patient had a flat-line response, without a change in the measured afferent pupillary defect at low-light intensity. This may reflect early saturation at illumination levels lower than that tested in the study. The eye with the relative afferent pupillary defect in that patient had normal foveal function with visual acuity of 20/20, 37-dB foveal threshold sensitivity, and normal Farnsworth-Munsell 100-Hue test. This may suggest that foveal function influences the initial increase in afferent pupillary defect despite marked, asymmetric visual field loss.[3]

The study confirmed that brighter light sources will produce a greater measured afferent pupillary defect, but a threshold level of illumination exists beyond which no further increase in afferent pupillary defect measurement will occur.[3] This suggests that a bright light source may be more useful for detecting subtle afferent pupillary defects, contrary to what has been suggested.[4] Additionally, luminance levels should be recorded because a change in the measured afferent pupillary defect may only reflect differing lighting conditions, rather than a true worsening or improvement of visual function.[5]

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Bleeding Complications in Thrombocytopenic Patients Undergoing Ophthalmic Surgery

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Bleeding complications from ocular surgery can range from a mild hyphema to massive spontaneous choroidal hemorrhage. Although bleeding complications can occur with any defect in the clotting cascade, thrombocytopenia, a disorder in which the platelet count is less than 100,000 cells/mm^3, is one predisposing factor. Since platelet counts are routinely performed before all surgical procedures at our institution, we studied the incidence of bleeding complications in ophthalmic surgical patients with thrombocytopenia.

During a one-year period at our institution, of 7,909 patients undergoing ophthalmic surgery 50 (0.6%) had thrombocytopenia. Of these 50 patients, three developed bleeding complications during or after ocular surgery. The bleeding complications included two patients with choroidal hemorrhages and one patient with a hyphema. In one patient the bleeding could have been predicted by the medical history of preleukemic syndrome. There was no history or clinical findings to suggest a bleeding disorder in the other two patients. Moreover, detection of a low platelet count contributed to the diagnosis of idiopathic thrombocytopenia in one of these two patients. A review of the 50 patients' medical records showed nine (22%) patients with a platelet count of less than 50,000 cells/mm^3. Two of these patients developed bleeding complications. Forty-one patients had a platelet count of 50,000 to 100,000 cells/mm^3. Of these patients, one developed bleeding complications.

The platelet counts (mean ± standard deviation) for those with bleeding complications (35,300 ± 23,700 cells/mm^3) was lower than that for patients without bleeding complications (79,500 ± 22,600 cells/mm^3). This difference was statistically significant ($P = .002$) by two sample Student's *t*-tests. All three patients with bleeding complications had platelet counts less than or equal to 55,000 cells/mm^3. Of the thrombocytopenic patients without bleeding complications, only seven of 47 patients (15%) had platelet counts less than 55,000 cells/mm^3. The 4% (two of 50 patients) incidence of choroidal hemorrhage in thrombocytopenic patients in our study is significantly higher ($P < .001$) than the 0.2% (110 of 55,735 patients) previously reported incidence of choroidal hemorrhage from cataract operations.[1]

Although our study indicates the risk of bleeding complications is low in patients with thrombocytopenia, this risk can be further reduced with correction of the platelet deficit. Appropriate treatment is determined by the cause of the thrombocytopenia. In patients with nonimmune-mediated thrombocytopenia, platelets can be transfused. In patients with immune-mediated thrombocytopenia, however, transfused platelets are destroyed rapidly, and medical treatment is warranted.

Extensive bleeding during surgery is rarely encountered when the platelet count exceeds 50,000 cells/mm^3.[2,3] Our data basically concur with these findings, although one patient did develop a hyphema at a platelet count of 55,000 cells/mm^3. Despite the low incidence of bleeding complications, the addition of a platelet count to a preoperative blood count is an inexpensive way to alert the surgeon to the potential of a preventable bleeding complication.

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Intracameral Tissue Plasminogen Activator for Treatment of Excessive Fibrin Response After Penetrating Keratoplasty

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We used intracameral tissue plasminogen activator for the treatment of an excessive fibrin response after penetrating keratoplasty in a 66-year-old man with insulin-dependent diabetes mellitus. The patient was referred to our institution for treatment of a *Pseudomonas* cor-

neal ulcer in the right eye. The patient was aphakic and had been wearing extended-wear soft contact lenses. He had a macular scar in the right eye and a repaired retinal detachment of the left eye. Visual acuity was R.E.: light perception and L.E.: 20/300. The keratitis gradually resolved. One month later, the right eye had a dense central corneal scar, hypotony, and a cyclitic membrane.

A penetrating keratoplasty, incision, and removal of the cyclitic membrane and anterior synechialysis was performed without operative complications. The postoperative course was complicated by a severe fibrin reaction that prevented visualization of the red reflex. Topical 1% prednisolone acetate hourly and oral prednisone (80 mg/day) was used in an attempt to minimize fibrin accumulation. The fibrin reaction persisted (Figure) and, on the third postoperative day, tissue plasminogen activator (25 μg) was injected into the anterior chamber. Four hours after the injection, there was a marked decrease in the fibrin, and the red reflex was apparent. Twenty-four hours after the injection, a small 5% layered hyphema was seen, the anterior chamber was deep, the graft was clear, and a red reflex was apparent. The aqueous had moderate flare and a plasmoid appearance but no formed fibrin. A near-total air-fluid exchange was performed. Six months later the patient's visual acuity had improved to R.E.: 20/300, as it was before the keratitis. There were 270 degrees of anterior synechiae and an intraocular pressure of R.E.: 10 mm Hg.

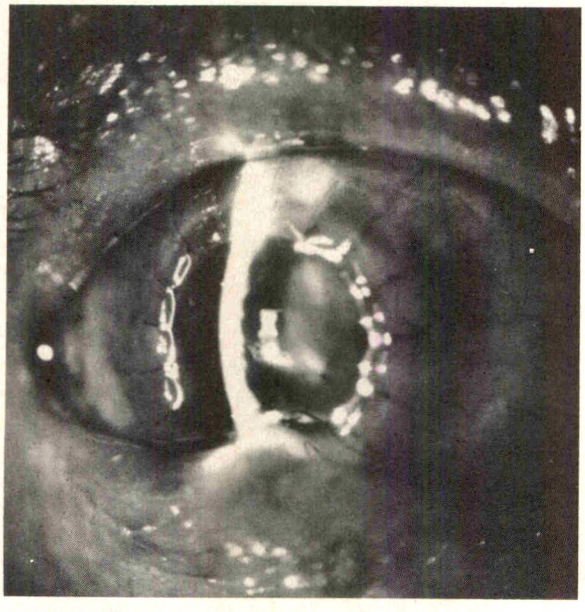

Figure (Snyder, Sherman, and Allinson). Slit-lamp photograph of the patient's right eye immediately before the intracameral tissue plasminogen activator injection.

Intraocular fibrin deposition is a serious complication of intraocular surgery.[1,2] Based on previously reported favorable experience in postvitrectomy patients,[1] we injected 25 μg of tissue plasminogen activator into the anterior chamber of our patient and noted prompt resolution of the fibrin. The dose used in this patient does not adversely affect corneal endothelial cell function.[3] Postoperatively, the patient has done well, with no recurrence of the cyclitic membrane. The cornea has remained clear, and he has had full recovery of his premorbid visual acuity.

Intracameral tissue plasminogen activator may be a safe and effective method to promote intraocular fibrinolysis. This modality of therapy may be a consideration for treating significant postoperative fibrin formation in patients who have had penetrating keratoplasty, anterior segment reconstruction, or both.

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Cold-Induced Corneal Edema as an Isolated Feature of Trigeminal Neuropathy

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Cold-induced corneal edema has been reported as a finding of trigeminal neuropathy.[1,2] In both of these cases, other sensory and motor features of trigeminal nerve dysfunction were apparent. We treated a patient in whom cold-induced corneal edema may have been an isolated feature of trigeminal neuropathy.

A 20-year-old man suffered traumatic left-sided optic neuropathy (no light perception), trigeminal sensory loss, abducens palsy, and facial nerve palsy after a motor vehicle accident in July 1988. Right-sided vision and trigeminal nerve function were normal. Progressive right-sided visual loss (visual acuity R.E.: 20/400) from compressive optic neuropathy caused by a traumatic carotid-cavernous fistula was documented seven months later (Fig. 1). Intra-arterial balloon occlusion of the internal carotid artery completely closed the fistula and visual acuity returned to R.E.: 20/20. No trigeminal nerve dysfunction occurred after this procedure.

In October 1989, the patient experienced painless fogging of vision within an hour of exposure to cold and wind. His vision returned to normal within 15 minutes after returning indoors. Examination showed visual acuity of R.E.: 20/15, normal cornea by slit-lamp biomicroscopy, and normal trigeminal motor and sensory function, including qualitative corneal sensation, on the right side. He noted foggy vision 20 minutes after an ice pack was placed over the right eye. Visual acuity was R.E.: 20/200, improving to R.E.: 20/30 with pinhole occlusion. The cornea showed mild stromal thickening. Fifteen minutes later, the symptom resolved, visual acuity returned to normal, and the stromal thickening had almost completely resolved. During another examination on a separate day, corneal thickness measured by ultrasonic pachymetry increased 0.57 mm on the right and 0.14 mm on the left in response to ice packs held over both eyes. Magnetic resonance imaging showed thrombosis of the right intra-

Fig. 1 (Jacobson, Willis, and Weinstein). Contrast enhanced computed tomography of the parasellar region in the coronal plane showing Meckel's cave on the left (black arrow). The enhancing mass on the right (black arrowheads), created by a carotid-cavernous fistula, has obliterated the anatomic landmark of Meckel's cave on that side.

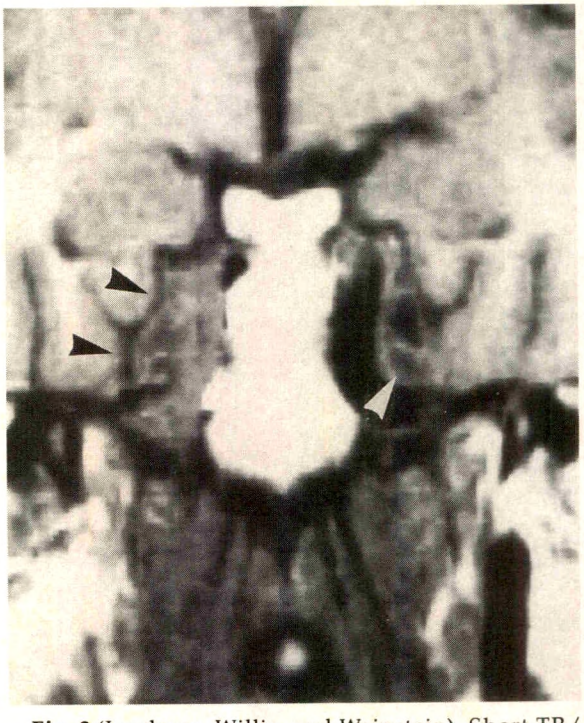

Fig. 2 (Jacobson, Willis, and Weinstein). Short TR/TE (resonance time/echo time) (500/20 msec) magnetic resonance image sequence using coronal orientation showing the normal low signal landmark of Meckel's cave on the left (white arrowhead). The carotid artery on the left is identified as the signal flow void passing under and medial to Meckel's cave. On the right, the anatomic definition of the contents medial to the dural border of the cavernous sinus (black arrowheads) and the region of Meckel's cave are ambiguous. The absence of signal flow void implies that the right carotid artery is thrombosed.

cavernous carotid artery, no fistula mass, and loss of anatomic definition of Meckel's cave on the right (Fig. 2).

We believe that his cold-induced corneal edema reflected previous trigeminal ganglion, or ophthalmic division, injury caused by fistula compression (Fig. 1). Perhaps, he did not notice this symptom during the fall and winter seasons after the accident because visual acuity was so impaired from optic nerve dysfunction.

Our case provides additional support for the localizing value of cold-induced corneal edema. This symptom should prompt an examination of the parasellar region by using magnetic resonance imaging,[3] regardless of whether other symptoms or signs of trigeminal neuropathy are apparent.

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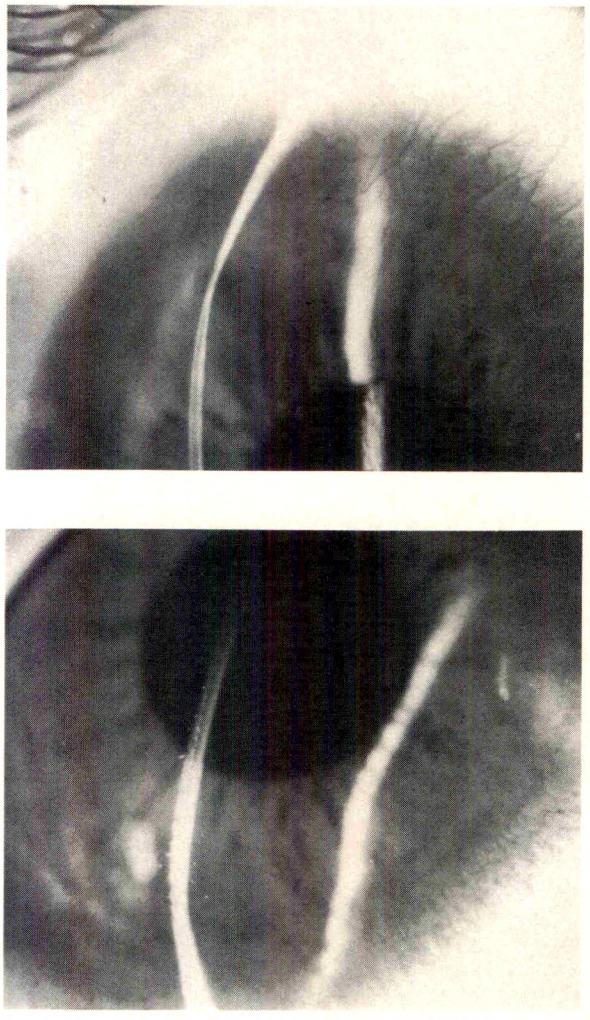

Fig. 1 (Cameron and Mahmood). Right eye. Top, Superior cornea is thin in a zone measuring 2 mm, approximately 2 mm from the corneoscleral limbus. Bottom, Inferior cornea shows mild thinning typical of pellucid marginal corneal degeneration.

Superior Corneal Thinning With Pellucid Marginal Corneal Degeneration

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Pellucid marginal corneal degeneration has been reported as a bilateral, clear, inferior, peripheral corneal-thinning disorder.[1] The cornea thins in an area measuring 1 to 2 mm, in a zone 1 to 2 mm from the corneoscleral limbus inferiorly, usually from the 4 o'clock to the 8 o'clock meridian on the cornea. Corneal protrusion occurs above the area of thinning. Keratoscopy shows a typical pattern of irregular, against-the-rule astigmatism with steepening of the inferior corneal periphery as indicated by the close proximity of the inferior rings on the keratoscopic photographs.

Kayazawa and associates[2] described 17 patients with pellucid marginal degeneration who also had keratoconus in the central part of the cornea. We treated a patient with bilateral superior corneal thinning in combination with pellucid marginal corneal degeneration.

An 11-year-old boy had gradual decrease in bilateral vision for one year. Uncorrected visual acuity was R.E.: 20/200 and L.E.: 20/125. Keratometric readings were R.E.: 46 at 165/37 at 65 and L.E.: 46 at 160/37 at 70. Slit-lamp examination (Fig. 1) showed bilateral, marked

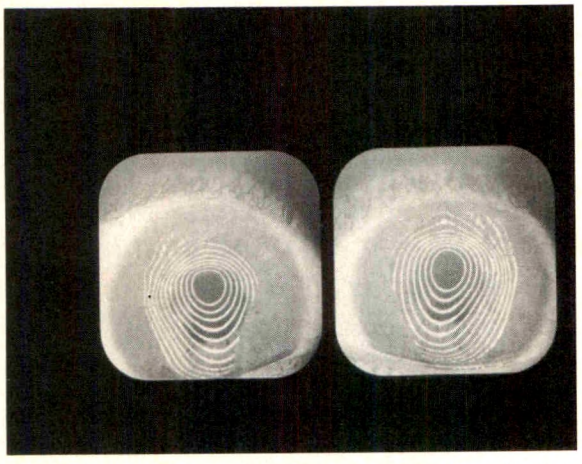

Fig. 2 (Cameron and Mahmood). Keratoscopic photograph shows bilateral irregular, against-the-rule astigmatism centrally, with inferior and superior peripheral steepening.

superior corneal thinning in a 2-mm zone approximately 2 mm from the corneoscleral limbus. Inferior, peripheral corneal thinning typical of pellucid marginal degeneration was also apparent in both eyes. On profile examination, both eyes showed superior protrusion of the cornea. Keratoscopic photographs (Fig. 2) showed central, irregular, against-the-rule astigmatism with inferior corneal steepening and marked superior corneal steepening. With spectacles of R.E.: -6.00 -3.00×85 and L.E.: -4.50 -6.00×75, the patient's visual acuity was 20/40 in each eye.

In a study of 61 patients with vernal keratoconjunctivitis and corneal ectasia, Cameron, Al-Rajhi, and Badr[3] noted that many patients had combinations of superior, central, inferior, or diffuse thinning of the cornea. Our patient showed the unusual combination of superior corneal thinning in association with pellucid marginal degeneration. There was no lipid infiltration suggestive of Terrien's peripheral corneal degeneration. Micropannus related to previous trachoma was apparent superiorly; however, the corneal thinning occurred in areas without vessels. There was no other associated ocular or systemic disease.

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Episcleritis and Symblepharon Associated With Lyme Keratitis

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A 42-year-old man who had a tick bite developed migratory arthritis, lethargy, and a large, red rash on his left leg. He was treated with ibuprofen and sulfasalazine, and his symptoms subsided. Two years later he developed arthralgias, fever, and blurred vision. According to his referring ophthalmologist, the patient had a bilateral nongranulomatous keratouveitis and secondary glaucoma. The keratitis consisted of scattered deep and superficial stromal infiltrates. An enzyme-linked immunosorbent assay for Lyme disease was 114 (normal = 101). A serum immunofluorescent antibody (IgM) titer to *Borrelia burgdorferi* was 1:128 (normal = 1:64). The patient was treated with topical timolol maleate and prednisolone acetate 1% and with intravenous ceftriaxone. He had complete resolution of joint pain, fever, and ocular symptoms. Six months later the patient was referred to the cornea service.

Visual acuity was R.E.: 20/20 and L.E.: 20/

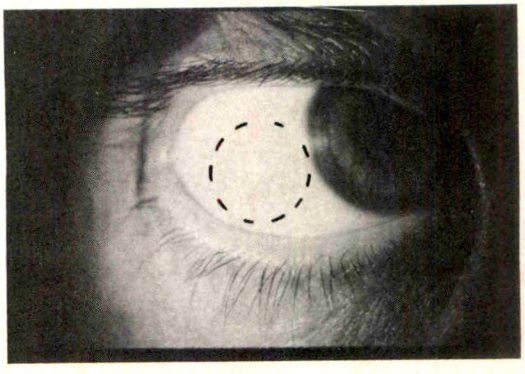

Fig. 1 (Zaidman). The broken circle outlines an area of mild episcleritis of the right eye.

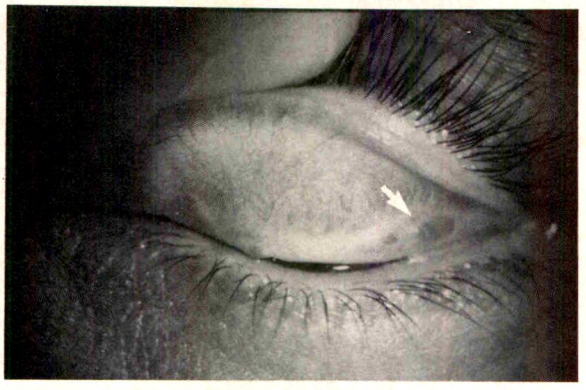

Fig. 2 (Zaidman). Symblepharon (arrow) in the temporal aspect of the left eye.

25. Both conjunctivae were uninflamed. Slit-lamp examination of the right eye was normal. Tarsoconjunctival scarring was apparent in the left upper and lower eyelids. The left cornea had many scattered subepithelial and anterior stromal infiltrates.

The patient was given a tapering regimen of fluorometholone eyedrops in both eyes. Six weeks later the patient reported that his eyes were comfortable and that vision had returned to normal. The patient discontinued the eyedrops. One month later the patient noted pain and foreign body sensation in the left eye and slight soreness in the right eye. Visual acuity was R.E.: 20/20 and L.E.: 20/30. A focal area of episcleritis was apparent in the inferotemporal quadrant of the right eye (Fig. 1). The left eye had the tarsoconjunctival scarring, and a symblepharon (Fig. 2) was noted between the temporal aspect of the left lower eyelid and the conjunctiva. The left cornea had some stromal infiltrates. Only the left eye was treated with fluorometholone. One month later the patient was asymptomatic.

As the incidence of Lyme disease has increased, there has been a corresponding increase in the number and variety of ocular manifestations.[1-3] This case indicates that episcleritis, conjunctival scarring, and symblepharon should be added to the list of the delayed ocular manifestations of Lyme disease.

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A Technique for Fixing Posterior Chamber Intraocular Lenses to the Iris Through a Corneoscleral Incision

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Various techniques for fixing posterior chamber lenses to the iris and ciliary body at the time of corneal transplantation when there is no posterior capsule to support the lens have been

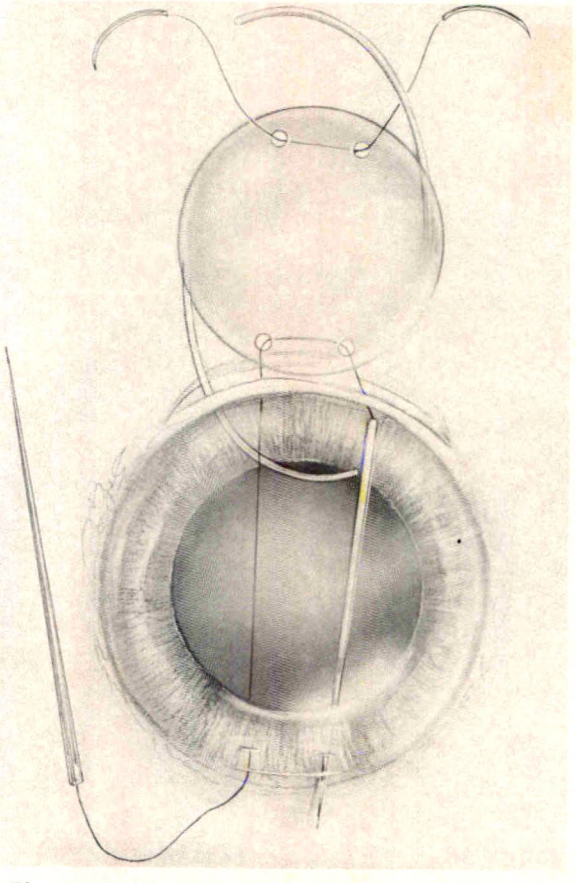

Fig. 1 (Navia). A 16-mm straight needle on a 10-0 Prolene suture is used to secure the intraocular lens to the back of the iris.

described.[1,2] Fixation by sutures to the ciliary body and sclera can be done through a corneoscleral incision.[3] Needle placement is difficult, hemorrhage from the ciliary body may occur, and other problems may occur. The intraocular lens may be fixed to the iris (Fig. 1) at the time of cataract surgery if the posterior capsule is lost, or the method may be used for secondary implantation in aphakic patients.

A posterior chamber lens with four perforating holes is held upside-down over the operative field by an assistant. A 10-0 Prolene suture with double-armed 16-mm straight needles is threaded through two adjacent holes, and the needles allowed to dangle. Another double-armed 10-0 Prolene suture with long, curved needles is threaded through the remaining two perforating holes. The straight needles are then passed one at a time into the anterior chamber, across the pupil, through the lower portion of the pupil, under the iris, and then through the peripheral iris stroma to emerge through the lower intact cornea.

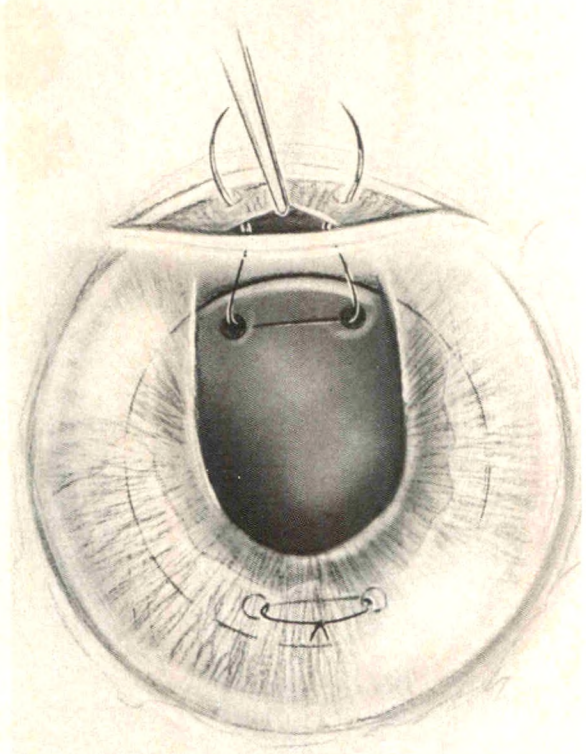

Fig. 2 (Navia). The lens is sutured to the iris using curved needles.

The curved needles are then passed into the anterior chamber, through the superior iris stroma, and through the corneoscleral incision out of the anterior chamber. The sutures are then gradually pulled up, and the intraocular lens introduced through the corneoscleral incision into the posterior chamber. The superior suture pair is tied on the iris surface and the ends trimmed (Fig. 2). The corneoscleral incision is then closed.

A small, 2-mm corneal incision is made near the area of exit of the lower pair of sutures. The needles are removed, an iris hook is used to engage the sutures within the anterior chamber, and to bring them out through the corneal incision. The sutures are then tied on the iris surface and the ends trimmed. The small inferior incision is closed with sutures, if necessary.

The depth of the anterior chamber is maintained throughout the procedure with air or a viscoelastic material.

This method avoids insertion of needles into the ciliary body, dissection of conjunctival and scleral flaps, and possible late exposure of suture knots.

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Posterior Subcapsular Cataracts Associated With Nasal or Inhalation Corticosteroids

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Department of Ophthalmology, Oregon Health Sciences University. This study was supported in part by a grant from Research to Prevent Blindness, Inc.

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The use of systemic,[1] topical ophthalmic,[2] or topical dermatologic[3] corticosteroids can cause posterior subcapsular cataracts. The National Registry of Drug-Induced Ocular Side Effects (Portland, Ore.) and the Committee on Safety of Medicines (London, England) have received reports of 21 patients with bilateral posterior subcapsular cataracts possibly associated with nasal aerosol or inhalation of beclomethasone dipropionate. These patients ranged in age from 16 to 72 years. Most of the patients had used beclomethasone dipropionate for more than five years, often in higher than the recommended dosages of 42 μg (one spray) in each nostril or 84 μg (two inhalations) three times daily (252 μg total). Nine of these patients were also receiving systemic corticosteroids.

The clinical potency of beclomethasone dipropionate is greater than that of other commonly used inhalation or nasal corticosteroids, such as dexamethasone, flunisolide, or triamcinolone. In reviewing the Registry's data, only one case of a patient with cataracts was found in association with any other nasally administered corticosteroids, namely dexamethasone in a patient who had used the drug for three years. Although beclomethasone dipropionate is thought to have a much reduced rate of systemic absorption from intranasal or inhalation routes of administration, oral ingestion may still occur. As with other topical ocular medication, the blood containing the drug is recirculated to the target organ, the eye, before being circulated to the detoxifying organs, liver, kidney, or both. This effect occurs with nasal-nasal pharynx absorption.[4] Although the systemic side effects of beclomethasone dipropionate are relatively mild, mental disturbances and suppression of hypothalamo-hypophyseal-adrenal system have been reported.[5] Although the role of nasal and inhalation corticosteroids in the development of cataracts is unclear, 15 cases of posterior subcapsular cataracts have been spontaneously reported to the Registry, which should alert ophthalmologists to the possibility of cataracts secondary to nasal administration or inhalation of corticosteroids.

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A Contraindication to Injection of Intravenous Fluorescein

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A 62-year-old woman had metamorphopsia in the left eye. Six years previously the patient had a right modified radical mastectomy (including axillary lymph node dissection) followed by local radiation therapy. Visual acuity was L.E.: 20/60 with central Amsler grid distortion. Examination of the left macula showed drusen and retinal pigment epithelium clumping. The patient subsequently underwent routine fluorescein angiography. The right antecubital vein was injected with 5 ml of 10% sodium fluorescein without apparent extravasation. No neovascular membrane was seen on angiography. Five days later the patient sought medical attention with her primary physician for fever, pain, swelling, and erythema of the right arm and forearm extending to and including the right hand and digits. The right arm had been normal since the mastectomy. Acute lymphangitis was diagnosed and oral antibiotic therapy was instituted. The patient did not improve after four days of therapy and was transferred back to our institution. The diagnosis of lymphangitis was confirmed. Edema and erythema of the right arm were noted. There was no evidence of phlebitis or localized urticaria to suggest fluorescein hypersensitivity. Intensive intravenous antibiotics, diuretics, compression, and physical therapy were used over the next

nine months with only partial resolution. A recent examination 53 months after the fluorescein injection demonstrated chronic right arm, forearm, and hand edema. A malpractice lawsuit including a significant financial award was settled in favor of the patient.

Local and systemic complications of fluorescein angiography have been reported.[1] Our patient was injected in the vein of an arm with surgically induced impaired lymphatic drainage without apparent dye extravasation. It is common clinical practice to avoid phlebotomy and intravenous line insertion into an extremity after regional lymph node dissection and removal, because even minor skin trauma can result in local cellulitis.[2] We believe the trauma of phlebotomy introduced skin flora into the subcutaneous tissue. This resulted in severe lymphangitis that subsequently led to local tissue edema and inflammation, further impairment of lymphatic drainage, and, ultimately, in severe, recalcitrant cellulitis because of compromised lymphatic drainage. Both the devastating outcome for this patient and the subsequent legal action could have been avoided by ascertainment of the medical history. We emphasize that the question of previous arm, breast, or axillary node surgery be routinely addressed before fluorescein angiography, and, further, that ipsilateral intravenous fluorescein injection is contraindicated in the clinical setting of compromised lymphatic drainage. If fluorescein injection is performed in a compromised extremity, it seems prudent to observe the patient closely on a daily basis and institute early referral to a specialist for definitive treatment to avoid complications.

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BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Cataract Surgery and Its Complications, ed. 5. By Norman S. Jaffe, Mark S. Jaffe, and Gary F. Jaffe. St. Louis, C. V. Mosby Company, 1990. 700 pages, index, illustrated. $120

Reviewed by ALAN SUGAR
Ann Arbor, Michigan

In their preface to the fifth edition of this classic text, the Jaffes state that "the technology of cataract surgery . . . has progressed at a blinding pace." The irony of the adjective is not wasted on those who have experienced the progress of the past few decades. Dr. Norman Jaffe certainly has the perspective to describe and critically evaluate this progress, to which he has been a major contributor. This book has almost doubled in size since the first edition of 1972. The emphasis has changed from intracapsular extraction to extracapsular extraction with intraocular lens insertion, but the principles of cataract surgical technique and complication prevention and management have been retained.

The first half of the text is devoted to surgical principles and techniques. Information on past methods, which those trained recently might consider outdated, must be understood to appreciate the current procedures and to understand that the accelerating course of change may never end, and will probably never reach perfection. The largest section discusses intraocular lens implants, and chapters on phacoemulsification and keratorefractive correction of aphakia are included. The phacoemulsification chapter is limited by its consideration of only the Kelman instrument. The brief section on pars plana lensectomy for routine cataract extraction is already outdated. In general these technical chapters are not step-by-step descriptions of specific techniques; they lean more toward the "what and why" than the "how" of cataract surgery. The chapter on postoperative corneal astigmatism is particularly good.

The second half of the book is devoted to complications of cataract extraction. These are not the cursory descriptions found in most texts, but are full, in-depth, well-referenced chapters on individual complications such as macular edema, endophthalmitis, glaucoma, corneal edema, and epithelial downgrowth. These chapters are updated to include recent advances. A minor error, however, is the repeated reference to the corneal endothelium being mesothelial, rather than neuroectodermal, in origin.

Throughout both sections of the book the illustrations, 1,057 photographs and drawings, are profuse and well done. This is a major ophthalmic text that should be well know to both fledgling and experienced cataract surgeons. It is not bound to the current fads and individual fancies that plague many texts, although many are included. It is an in-depth didactic coverage of the most important ophthalmic surgical procedures. I still referred to my 1972 edition until I read this edition, which will also have lasting value.

Aesthetic Surgery of the Eyelids. By Raul Loeb. New York, Springer-Verlag, 1989. 155 pages, index, illustrated. $175

Reviewed by JOHN A. LONG
Birmingham, Alabama

Raul Loeb, an eminent general plastic surgeon of São Paulo, Brazil, offers an insightful view of his approach to the patient undergoing blepharoplasty, the techniques of blepharoplasty, and the management of complications.

Dr. Loeb emphasizes topographic analysis of the various contours of the periorbital region. Figures illustrate the contributions of periocular anatomy to surface characteristics. Abnormal contours are divided into bulges of the skin, fat, muscle, and bone. The goal of surgery is to create "flat surfaces," which Loeb believes is the "aesthetic ideal." The highlight of the volume is the chapter on eyelid depressions. The author describes the techniques of autogenous fat transplants and sliding fat transpositions that he has developed over the last 20 years.

The author deals extensively with the problem of scleral show and ectropion after lower eyelid blepharoplasty. The best treatment of these problems is prevention. A section of the text concerns the preoperative recognition of patients who may be predisposed to lower eyelid complications after blepharoplasty. Many ophthalmologists who treat patients with corneal exposure will disagree with the statement that scleral show after blepharoplasty is "only

an aesthetic problem." The treatment proposed for lower eyelid scleral show and ectropion is limited to skin grafting. The techniques of transconjunctival lower eyelid blepharoplasty and lateral canthal tightening with subcutaneous dissection of cicatricial bands are not mentioned.

This book is an important contribution to the field of blepharoplasty surgery. Since eyelid surgery is performed by surgeons from many disciplines, it is always informative to read about different approaches to the operation. Ophthalmologists who perform blepharoplasty will find the author's approach and the treatment of complications enlightening.

Laser Microsurgery of Glaucoma. By Lucio Buratto, Alberto Ricci, and Daniele Vitali. Milan, Fogliazza Editore, 1988. 247 pages, illustrated. $120

Reviewed by WALLACE L. M. ALWARD
Iowa City, Iowa

The aim of this attractive book is to explain the various laser techniques used in the treatment of glaucoma. It is divided into three sections. The first section describes aqueous dynamics, examination methods, and laser basics. The middle section, the focus of the text, discusses the major laser techniques in some depth. The last section discusses the therapy of various types of glaucomas, with an emphasis on the use of the laser.

The book is beautifully illustrated by Bianca Manfredi. The section devoted to laser techniques covers all of the laser procedures used in glaucoma treatment. The authors clearly describe their own methods as well as those of others. Although the techniques section is thorough, the rest of the book is sometimes superficial. A three-page chapter on perimetry hardly does the subject justice.

If using this text as a springboard to further study, the student may be disappointed. Statements such as "according to some authors" are not referenced, leaving the reader to take these declarations on faith. Even papers heavily borrowed from, such as the gonioscopic grading system of Scheie, are neither referenced nor credited in the bibliography. The book has no index.

This book would best serve the needs of someone wanting a "how-to" guide to glaucoma laser therapy. The descriptions of techniques are usually clear and the illustrations are terrific.

The Vitreous. Structure, Function, and Pathobiology. By J. Sebag. New York, Springer-Verlag, 1989. 173 pages, index, illustrated. $69

Reviewed by JOSE S. PULIDO AND THOMAS K. SHIRES
Iowa City, Iowa

This book is a clear summary of the biology and pathology of the vitreous. The first six chapters cover in detail the basic science required for an understanding of the vitreous. The last chapter explains that it is not possible to discuss the various diseases affecting the vitreous without some understanding of the ideas covered in the first six chapters.

The references at the end of each chapter are complete, up-to-date, and include historical as well as pertinent non-English references. This text is a good starting point for basic scientists interested in vitreoretinal disease and for ophthalmologists with a special interest in vitreoretinal research. We have both learned a lot from this book, and we recommend it to all interested investigators.

What Kind of Life. The Limits of Medical Progress. By Daniel Callahan. New York, Simon & Shuster, 1990. 318 pages, index. $19.95

Reviewed by FRANK W. NEWELL
Chicago, Illinois

This volume contains the familiar theme that health care costs in the United States far exceed similar costs of other countries, that 37 million citizens lack health insurance, that the death rate has declined, but that the increase in the number of elderly has been accompanied by an increase in the number of chronic conditions requiring medical care and advanced technology. Predictably, Callahan advocates rationing medical care but with a difference that rarely appears in print: stop saving babies with birth weights of less than 500 g and stop special medical care for those more than 80 years old.

One chapter is devoted to euthanasia, assisted suicide, killing, and allowing to die. Attention is not directed to the likelihood that those who can pay will continue to receive modern medicine and once again the poor will suffer

from the ravages of health planning. The problems of malnutrition, poor housing, near illiteracy, drug use, pollution, crime, and related social ills that relate to many of the costs of medical care are not addressed. Those who would debate these topics should surely be familiar with the author's premises.

Books Received

Proliferative Vitreoretinopathy. Edited by K. Heimann and P. Wiedemann. Heidelberg, Germany, Kaden Verlag, 1989. Softcover, 327 pages, illustrated.

This is the Proceedings of the International Symposium on Proliferative Vitreoretinopathy held in Koln in September 1988. Seventy papers are offered, grouped under ten headings: Incidence, Animal Models, Pathology, Cell Biology, Clinical Pathology, Vitreous Substitutes, Surgery, Medical Treatment, Instruments, and Miscellany.

Retinal Detachment and Vitreous Surgery. By H. Richard McDonald, Howard Schatz, and Robert N. Johnson. The Retina Research Fund. San Francisco, 1989. 67 pages, illustrated. $4

Patients and their families will appreciate this series of educational booklets. Where else can they find information about macular degeneration and diabetic retinopathy? This third booklet in the series has more and better illustrations than the first two and should help to answer patients' questions.

Sensory Systems I. Vision and Visual Systems. Edited by Richard Held. Boston, Birkhauser, 1988. Softcover, 133 pages, illustrated. $24.50

The Encyclopedia of Neuroscience is a compendium of more than 700 articles covering all areas of neuroscience. Richard Held, professor of psychology at Massachusetts Institute of Technology, has selected 49 of these articles that discuss vision and the visual system (its anatomy, physiology, and pathology; its psychophysics and behavior; and its development and plasticity), and reprinted them in this softcover book. It should make fascinating reading for anyone interested in the visual system because in each article an expert has tried to clarify and condense a small group of related ideas into a page or two.

The Book List

Current Ocular Therapy 3. Edited by Frederick T. Fraunfelder and F. Hampton Roy. Philadelphia, W. B. Saunders Company, 1990. 792 pages, index. $80

Manual of Fundus Fluorescein Angiography. By Amresh Chopdar. Boston, Butterworths, 1989. 134 pages, index, illustrated. $72

Microsurgery of Retinal Detachment, ed. 2. By Mireille Bonnet. New York, Field & Wood Medical Publishers, Inc., 1989. 313 pages, index, illustrated. $120

Ocular Toxicology. Proceedings of the First Congress of the International Society of Ocular Toxicology. Edited by Sidney Lerman and Ramesh C. Tripathi. New York, Marcel Dekker, Inc., 1990. 420 pages, index, illustrated. $99.75

Ophthalmic Surgery. Principles and Practice, ed. 2. Edited by George L. Spaeth. Philadelphia, W. B. Saunders Company, 1990. 776 pages, index, illustrated. $125

Providing Services for People With Vision Loss. A Multidisciplinary Perspective. Edited by Susan L. Greenblatt. Lexington, Massachusetts, Resources for Rehabilitation, 1989. Softcover, 136 pages, illustrated. $19.95

The Retinoscopy Book. A Manual for Beginners, ed. 3. By John M. Corboy. Thorofare, Slack Inc., 1989. Softcover, 123 pages, index, illustrated. $35

Surgical Intervention in Corneal and External Disease. By Richard L. Abbott. San Francisco, Continuing Ophthalmic Video Education Committee of the American Academy of Ophthalmology, 1990. Videotape.

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

Annals of Internal Medicine

Systemic effects of medications used to treat glaucoma. Everitt, D. E., Avorn, J. (Beth Israel Hosp., Prog. for the Analysis of Clin. Strategies, 330 Brookline Ave., Boston, MA 02115). Ann. Intern. Med. 112:120, 1990.

Medications used to treat glaucoma can have clinically important systemic effects in some patients; these effects may not be recognized in elderly patients who have chronic medical problems and who are taking several systemic medications. Beta-blocking ophthalmic agents are generally safe, but can be absorbed systemically to induce bronchospasm, worsen heart block, decompensate congestive heart failure, or create central nervous system effects in some patients. Reports of adverse systemic effects from miotics, such as pilocarpine, are rare, although cardiovascular decompensation has been seen in patients with acute angle closure who were given excessive doses before surgery. Topical sympathomimetic agents such as epinephrine may increase ventricular extrasystoles and have, on occasion, caused severe hypertensive reactions. Nearly 50% of patients taking carbonic anhydrase inhibitors must discontinue their use because of various adverse constitutional and central nervous system symptoms. Although these drugs are not usually part of internal medicine regimens, they can produce adverse effects that mimic primary disease in nonocular organ systems. (1 table, 48 references)—Authors' abstract

Australian and New Zealand Journal of Ophthalmology

Vogt-Koyanagi-Harada syndrome — isolation of cloned T cells with specificity for melanocytes and melanoma cells. McClellan, K. A., MacDonald, M., Hersey, P., and Billson, F. A. (Sydney Eye Hosp., Woolloomooloo, NSW 2011, Australia). Aust. N.Z. J. Ophthalmol. 17:347, 1989.

Immunologic studies were done on two patients who had Vogt-Koyanagi-Harada syndrome. In the first patient antibodies to melanoma cells in cytotoxic assay were detected, which may indicate the presence of antibodies to melanocytes. In the second patient three clones of interleukin-2-dependent T cells were isolated which appeared to have specificity in both cytotoxic and proliferative assays to cultured normal melanocytes and to three allogenic melanoma cells. These findings further support a role for autoimmunity to pigmented cells in the pathogenesis of Vogt-Koyanagi-Harada syndrome. (3 tables, 24 references)—Ronald Lowe

British Journal of Ophthalmology

Human fetal iridocorneal angle: a light and scanning electron microscopic study. McMenamin, P. G. (Dept. Anatomy and Hum. Biol., Univ. Western Australia, Nedlands, Perth 6009, Western Australia). Br. J. Ophthalmol. 73:871, 1989.

The authors studied eyes from fetuses with gestational ages of 12 to 22 weeks. Early in gestation corneal endothelium may extend almost to the angle apex but this lining is perforated by discrete intercellular gaps. As development progresses the uveal trabecular endothelial cells are morphologically distinguishable from the corneal endothelial cells. The trabecular endothelium has numerous gaps that increase in size, are well developed by 18 to 20 weeks, and provide a clear route of communication between the fetal anterior chamber and the developing intercellular spaces of the trabecular tissue. In no eye was an uninterrupted endothelial membrane present. Thus, it seems unlikely that congenital glaucoma is caused by persistent endothelial pretrabecular meshwork. (4 figures, 1 table, 28 references)—David Shoch

Clinical parameters predictive of enlargement of melanocytic choroidal lesions. Augsburger, J. J., Schroeder, R. P., Territo, C., Gamel, J. W., and Shields, J. A. (Retina Ser., 9th & Walnut Sts., Philadelphia, PA 19107). Br. J. Ophthalmol. 73:911, 1989.

The authors divided 197 melanotic choroidal lesions into four groups. Sixty-two were benign nevi, 76 were classified as suspicious nevi, 41 as dormant melanomas, and 18 as active melanomas. All these lesions were untreated and followed up for a five-year period. Thirty-nine of the lesions enlarged. The most significant predictors for enlargement were thickness of the lesion, the presence of a retinal detachment, and symptoms. The five-year incidence of enlargement of lesions for patients with none of these predictors was 5.8%, whereas for patients who had all three characteristics the likelihood of enlargement was 90.6%. (5 figures, 3 tables, 12 references)—David Shoch

Cancer Genetics and Cytogenetics

First cytogenetic evidence of homozygosity for the retinoblastoma deletion in chromosome 13. Lemieux, J., Milot, J., Barsoum-Homsy, M., Michaud, J., Leung, T. K., and Richer, C. (Department d'anatomie, Faculte de Medecine, Universite de Montreal, C.P. 6128, Succ. A, Montreal, Quebec, H3C 3J7, Canada). Cancer Genet. Cytogenet. 43:73, 1989.

The retinoblastoma gene was the first described antioncogene, and unlike other cancer genes, causes cancer by its absence rather than by its hyperactivity. Early studies assigned the gene to region I of band 4 of chromosome 13 along with the esterase D gene. A heterozygotic lesion in that region is associated with a high risk of developing retinoblastoma. Homozygosity of the lesion, the so called "two-hit mutation model" postulated by Knudson, was proposed to account for the development of the tumor. Since the retinoblastoma gene is recessive it seems that both normal alleles must be lost as a prerequisite for tumor formation. The authors used high-resolution cytogenetics of a retinoblastoma tumor to disclose a homozygotic lesion in bands q13.3–14.2 of chromosome 13 in 35% of the cells and a heterozygotic lesion in the same region in 17%. This provides the first cytogenetic evidence of the two somatic mutations considered essential to activate the retinoblastoma gene. (2 figures, 44 references)—David Shoch

Journal of Internal Medicine

Nephropathy is delayed by intensified insulin treatment in patients with insulin-dependent diabetes mellitus and retinopathy. Reichard, P., and Rosenqvist, U. (Dept. Intern. Med., Sodersjukhuset, S-100 64 Stockholm, Sweden). J. Intern. Med. 226:81, 1989.

One hundred two patients with insulin-dependent diabetes mellitus and nonproliferative retinopathy were randomly assigned to two groups. Ninety-five were available for study after three years. Forty-four of the patients were given an intensified conventional insulin treatment with home blood glucose monitoring and multiple daily insulin injections. Fifty-one patients continued the same treatment they had been receiving before the study. Glycosylated hemoglobin levels were markedly reduced in the intensive insulin treatment group as compared to the regular treatment group ($P = .00001$). Manifest nephropathy after three years was seen almost exclusively in patients with glycosylated hemoglobin levels above 9%. Thus, improved blood glucose control delayed the progression of nephropathy in patients with insulin-dependent diabetes mellitus and retinopathy. (3 figures, 2 tables, 21 references)—David Shoch

Nature

A point mutation of the rhodopsin gene in one form of retinitis pigmentosa. Dryja, T. P., McGee, T. L., Reichel, E., Hahn, L. B., Cowley, G. S., Yandell, D. W., Sandberg, M. A., and Berson, E. L. (Harvard Med. School, Massachusetts Eye & Ear Infirm., 243 Charles St., Boston, MA 02114). Nature 343:364, 1990.

Retinitis pigmentosa occurs in the United States in approximately one of 3,500 births. In a study done in Maine, somewhat less than half of the cases were transmitted as an autosomal dominant trait, 20% were autosomal recessive, 8% were X-linked, and 23% were isolated cases. The authors examined members of a large pedigree of Irish origin and found an abnormality in the long arm of chromosome 3. This arm contains the gene coding for rhodop-

sin. The fundamental defect is a change of the amino acid proline to a histadine residue at position 23. Thus, for the first time a specific form of autosomal dominant retinitis pigmentosa can be diagnosed specifically and patients who have such a gene defect can be told they have a 50% chance of passing on the defect to their children. (4 figures, 1 table, 25 references)—David Shoch

Neurology

"Transient monocular blindness" versus "amaurosis fugax." Fisher, C. M. (Neurol. Ser., Massachusetts Gen. Hosp., Boston, MA 02114). Neurology 39:1622, 1989.

The author objected to the use of the vague term "amaurosis fugax" as a substitute for the more specific term "transient monocular blindness." When amaurosis fugax is used it must be further defined as unilateral or bilateral and cannot be easily conjoined with recurrent or intermittent. Further, it is a Greek and Latin hybrid and requires definition for those not acquainted with the subject. Transient monocular blindness is the older term and has the advantage of being specific and clear. Finally, the author points out that the amaurosis is a subject heading which was dropped by the Index Medicus in 1936 and replaced by "blindness," a practice that has continued to the present. (36 references)—David Shoch

New England Journal of Medicine

Cancer-associated retinopathy (car syndrome) with antibodies reacting with retinal, optic-nerve, and cancer cells. Thirkill, C. E., FitzGerald, P., Sergott, R. C., Roth, A. M., Tyler, N. K., and Keltner, J. L. (Dept. Ophthalmol., 1603 Alhambra Blvd., Sacramento, CA 95816). N. Engl. J. Med. 321:1589, 1989.

The occurrence of visual loss in association with distant carcinoma has been the subject of numerous reports. Visual loss occurs in the absence of any direct invasion of the visual system by the neoplasm. The most common associated neoplasm is the small cell carcinoma of the lung. This distant effect in the absence of metastases is called a paraneoplastic phenomenon. The patient described in this report lost vision in both eyes and was eventually found to have a small cell carcinoma of the lung. Biopsy specimens of the meninges surrounding the optic nerves did not demonstrate infiltration. Serum samples disclosed high titers of antibodies against ocular antigens including retinal and optic nerve proteins. Plasmapheresis reduced the antibody titers to retina and optic nerve but did not benefit the patient's declining vision. There seems to be a relationship between small cell carcinoma of the lung, activated antinuclear immunologic response, and loss of vision. If this is the result of an autoimmune process it might be appropriate to institute site-specific immunosuppressive therapy to alter the course of the remote ocular effects associated with cancer. (6 figures, 2 tables, 40 references)—David Shoch

Oncogenic point mutations in the human retinoblastoma gene: their application to genetic counseling. Yandell, D. W., Campbell, T. A., Dayton, S. H., Petersen, R., Walton, D., Little, J. B., McConkie-Rosell, A., Buckley, E. G., and Dryja, T. P. (Howe Lab., Massachusetts Eye & Ear Infirm., 243 Charles St., Boston, MA 02114). N. Engl. J. Med. 321:1689, 1989.

One of the major problems in the management of retinoblastoma is the difficulty in determining whether a particular patient has a hereditary or nonhereditary form of the disease. An estimated 40% of patients have a manifestation of hereditary retinoblastoma but only one fourth of these have a family history of the disease. The remainder are affected by new mutations of the germ cells. This combination of new germ cell mutations and the large portion that originate from nonhereditary somatic mutations make it uncertain whether a particular patient has the hereditary or the nonhereditary form of the disease and whether the relatives are carriers of a new hereditary mutation. Another complicating feature is the failure of retinoblastoma to develop in approximately 10% of all obligate carriers with germ line mutation. The authors developed a sensitive technique of DNA sequence analysis to identify mutations as small as a single nucleotide chain in tumors from seven patients with retinoblastoma but no family history. In four patients the

mutation involved only the tumor cells and in three patients it involved normal somatic cells and tumor cells but was not found in either parent. Therefore, these mutations must be new germ cell mutations. The technique they describe therefore can distinguish hereditary from nonhereditary retinoblastoma, which is important for genetic counseling and for clinical evaluation of other members of the family. (3 figures, 2 tables, 51 references)—David Shoch

Ophthalmologica

Light and electron microscopic findings in Leigh's disease. Kremer, I., Lerman-Sagie, T., Mukamel, M., Sandbank, J., Nissenkorn, I., and Mimouni, M. (Dept. Ophthalmol., Beilinson Med. Ctr., 49100 Petah Tiqva, Israel). Ophthalmologica 199:106, 1989.

Leigh's disease is a mitochondrial enzymatic deficiency in which infants show progressive neurologic deterioration leading to death from respiratory arrest. The ocular findings are similar to those seen in the Kearns-Sayre syndrome, another mitochondrial disorder. In the pigmentary retinal degeneration of Kearns-Sayre syndrome, there are enlarged mitochondria with pericrystalline inclusions in cells throughout all retinal layers. In the patient in this study with Leigh's disease, additional findings were macular epiretinal membranes and numerous large macrophages filled with PAS-positive material, which may have been material released from disintegrating mitochondria. (6 figures, 12 references)—David Shoch

Retina

Neurosyphilis and ocular syphilis in patients with concurrent human immunodeficiency virus infection. Levy, J. H., Liss, R. A., and Maguire, A. M. (315 E. Quadrangle Bldg., Village of Cross Keys, Baltimore, MD 21210). Retina 9:175, 1989.

Two patients with ocular lesions had human immunodeficiency virus infection neurosyphilis. Apparently in the presence of human immunodeficiency virus infection the spirochete acts like an opportunistic invader and rapidly causes neurosyphilis, a complication that usually occurs in only 3% of patients with syphilis. Eleven of 13 patients with both ocular syphilis and concurrent human immunodeficiency virus infections had neurosyphilis. The authors recommend that all patients who are seropositive for syphilis be tested for human immunodeficiency virus infection and all patients who are seropositive for the human immunodeficiency virus be tested for syphilis. If both infections are present then spinal fluid examination for neurosyphilis should be undertaken. (4 figures, 1 table, 22 references)—David Shoch

Acute macular neuroretinopathy following intravenous sympathomimetics. O'Brien, D. M., Farmer, S. G., Kalina, R. E., and Leon, J. A. (Dept. Ophthalmol., RJ-10, Univ. Washington, Seattle, WA 98195). Retina 9:281, 1989.

Three women in their middle 20s were given intravenous ephedrine (one patient) or epinephrine (two patients). In two patients blood pressure increased markedly. The blood pressure was not measured in the third patient. All of the patients developed bilateral paracentral scotomas. Each showed peculiar red, wedge-shaped lesions surrounding the foveola, which appeared to be located in the outer retina and corresponded to the paracentral scotomas on Amsler grid testing. The appearance of the lesions was apparently caused by changes in retinal contour after atrophic thinning of the retina. (7 figures, 11 references)—David Shoch

Correction

In the article, "Effects and interactions of epinephrine, norepinephrine, timolol, and betaxolol on outflow facility in the cynomolgus monkey" (Am. J. Ophthalmol. 109:189, February 1990), by J. C. Robinson and P. L. Kaufman, Table 1 contained an error in the column labeled "Treated Group." The corrected table is reprinted below.

TABLE 1

TOTAL OUTFLOW FACILITY AFTER THE UNILATERAL ADMINISTRATION OF ADRENERGIC DRUGS*

DRUG (DOSE [μG], ROUTE)	NO. OF ANIMALS	TREATED GROUP	CONTROL GROUP	TREATED GROUP/CONTROL GROUP
Epinephrine (600, topical)	8	0.46 ± 0.10	0.36 ± 0.09	1.33 ± 0.11†
Epinephrine (600, topical)‡	7	0.43 ± 0.10	0.33 ± 0.08	1.32 ± 0.09§
Epinephrine (10, intracameral)	8	0.85 ± 0.26	0.50 ± 0.13	1.69 ± 0.24†
Norepinephrine (10, intracameral)	9	0.43 ± 0.05	0.30 ± 0.05	1.65 ± 0.22 ‖
Timolol (180, topical)	6	0.30 ± 0.06	0.29 ± 0.03	1.03 ± 0.07
Betaxolol (180, topical)	6	0.24 ± 0.03	0.27 ± 0.06	0.99 ± 0.10

*Facility data are mean ± S.E.M. $\mu l \times min^{-1} \times mm\ Hg^{-1}$. Facility measurements encompassed hours 3.25 through 4.0 after dosing.

†Significantly different from 1.0 by the two-tailed paired *t*-test: P = .03.

‡Epinephrine given twice daily, facility measured on day 4.

§Significantly different from 1.0 by the two-tailed paired *t*-test: P = .01.

‖Significantly different from 1.0 by the two-tailed paired *t*-test: P = .02.

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International Agency for the Prevention of Blindness: Fourth General Assembly

The International Agency for the Prevention of Blindness will hold its Fourth General Assembly Nov. 11–16, 1990, in Nairobi, Kenya. For further information, write IAPB Coordinating Committee, c/o Ad-Venture Promotions Ltd., P.O. Box 11505, Nairobi, Kenya.

VII International Orthoptic Congress: Advances in Strabismus and Amblyopia

The VII International Orthoptic Congress: Advances in Strabismus and Amblyopia will be held June 2–6, 1991, in Nürnberg, West Germany. Registration forms are available in German, English, and French for the submission of papers and posters. For further information, write Office of the Congress Organizing Committee, Dr.-Kurt-Schumacher-Str. 12, D-8500 Nürnberg 1, Federal Republic of Germany.

IX International Perimetric Society Meeting

The IX International Perimetric Society Meeting will be held June 17–20, 1990, in Malmö, Sweden. For further information, write IX Meeting Secretariat, Department of Ophthalmology, University of Lund, Malmö General Hospital, S-214 01 Malmö, Sweden.

A. Z. Middelheim—Antwerp: Intraocular Trauma Course

A. Z. Middelheim, Department of Ophthalmology, will hold an Intraocular Trauma Course Oct. 1–3, 1990, in Antwerp, Belgium. For further information, write Mrs. D. Verhoeven, Course Secretary, Department of Ophthalmology, A. Z. Middelheim, Lindendreef 1, 2020 Antwerp, Belgium.

Cleveland Clinic Foundation: XIX Annual Ophthalmology Symposium

The Cleveland Clinic Foundation: XIX Annual Ophthalmology Symposium will be held June 1 and 2, 1990, in Cleveland, Ohio. For further information, write Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Ave., Rm. TT-31, Cleveland, OH 44195-5241; telephone (800) 762-8173 (national), (800) 762-8172 (Ohio).

Colby College: Annual Kevin Hill Seminar

The Colby College will hold the Annual Kevin Hill Seminar in Ophthalmology focusing on glaucoma and glaucoma surgery, July 22–26, 1990. For further information, write R. H. Kany, Director of Special Programs, Colby College, Waterville, ME 04901; telephone (207) 872-3386.

Hawaii Ophthalmological Society: 1990 Officers

The Hawaii Ophthalmological Society 1990 officers are as follows: George Plechaty, president; John H. Drouilhet, vice president; Jorge G. Camara, secretary; Jon M. Portis, treasurer; and Calvin M. Miura, member-at-large.

University of Illinois at Chicago: Third Annual Contact Lens Course—Update for the 1990s

The University of Illinois at Chicago: Third Annual Contact Lens Course—Update for the 1990s will be held June 22 and 23, 1990, in Chicago. For further information, write Contact Lens Conference Registrar, UIC Conferences and Institutes, Box 6998, Chicago, IL 60680; telephone (312) 996-5225.

Humana Hospital Audubon: Seventh Annual Ophthalmology Seminar—Ophthalmic Insights Into the 90s

The Seventh Annual Humana Hospital Audubon Ophthalmology Seminar: Ophthalmic Insights Into the 90s will be held Sept. 22, 1990, at Humana Hospital Audubon in Louisville, Kentucky. For further information, write Nor-

man D. Radtke, 240 Audubon Medical Plaza, Louisville, KY 40217; telephone (502) 636-2823.

Long Island Jewish Medical Center and North Shore University Hospital: A Clinical Day in Ophthalmology

The Long Island Jewish Medical Center Department of Ophthalmology and the North Shore University Hospital Department of Ophthalmology will sponsor a Clinical Day in Ophthalmology on Ocular and Orbital Trauma, May 23, 1990, in Garden City, New York. For further information, write Ann J. Boehme, CMP, Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park, NY 11042; telephone (718) 470-8650.

Manhattan Eye, Ear and Throat Hospital: Postgraduate Course—Pediatric Ophthalmology and Strabismus Update, 1990

The Manhattan Eye, Ear and Throat Hospital: Postgraduate Course—Pediatric Ophthalmology and Strabismus Update, 1990, sponsored by the Department of Ophthalmology, will be held May 5, 1990, in New York City. For further information, write Francine Leinhardt, Course Coordinator, Manhattan Eye, Ear and Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 838-9200, ext. 2776.

Mount Sinai School of Medicine: Cosmetic Surgery of the Aging Eye

The Mount Sinai School of Medicine: Cosmetic Surgery of the Aging Eye will be held June 22 and 23, 1990, in New York City, New York. For further information, write Post-Graduate School, Box 1193, Mount Sinai School of Medicine, One Gustave Levy Place, New York, NY 10029; telephone (212) 241-6737.

University of Medicine & Dentistry of New Jersey—New Jersey Medical School: Symposium on Immunologic Disorders of the Visual System

The University of Medicine & Dentistry of New Jersey—New Jersey Medical School: Symposium on Immunologic Disorders of the Visual System will be held May 7 and 8, 1990, at Bally's Grand Hotel, Atlantic City, New Jersey. For further information, write Patricia Sarles, Department of Continuing Medical Education, UMDNJ-New Jersey Medical School, 185 S. Orange Ave., Newark, NJ 07103-2757; telephone (201) 456-4267.

Pacific Presbyterian Medical Center and Pacific Vision Foundation: Corneal and Refractive Surgery—A Symposium Commemorating Max Fine, M.D.

Pacific Presbyterian Medical Center and Pacific Vision Foundation: Corneal and Refractive Surgery—A Symposium Commemorating Max Fine, M.D., will be held Sept. 21 and 22, 1990, in San Francisco, California. For further information, write Joni Beemsterboer, Administrative Coordinator, Pacific Vision Foundation, 2340 Clay St., #124, San Francisco, CA 94115; telephone (415) 923-3423.

Mericos Eye Institute of Scripps Memorial Hospitals: Visions in Ophthalmology '90

The Mericos Eye Institute of Scripps Memorial Hospitals: Visions in Ophthalmology '90 will be held May 11 and 12, 1990, in La Jolla, California. For further information, write Mericos Eye Institute of Scripps Memorial Hospitals, P.O. Box 28, La Jolla, CA 92038; telephone (619) 453-6222.

Stanford University: Basic Science Course in Ophthalmology

The Stanford University: Basic Science Course in Ophthalmology will be held July 2 through August 31, 1990, in Stanford, California. For further information, write Peter R. Egbert, M.D., Department of Ophthalmology, A-157, Stanford Medical Center, Stanford, CA 94305-5308; telephone Susan March (415) 725-7269.

UCLA School of Medicine—Jules Stein Eye Institute: Ocular Oncology Course

The UCLA School of Medicine—Jules Stein Eye Institute: Ocular Oncology Course will be held May 11, 1990, in Los Angeles, California. For further information, write Gretchen Falvo, Director of Academic Programs, Jules Stein Eye Institute, 100 Stein Plaza, UCLA, Los Angeles, CA 90024-7000; telephone (213) 825-4617.

University of Washington, Department of Ophthalmology: 16th Annual Resident Alumni Day

The University of Washington, Department of Ophthalmology: 16th Annual Resident Alumni Day will be held on June 2, 1990, in Seattle,

Washington. For further information, write Richard P. Mills, M.D., Department of Ophthalmology, University of Washington (RJ-10), Seattle, WA 98195.

Washington University School of Medicine: Third Annual Contact Lens Course

The Washington University School of Medicine: Third Annual Contact Lens Course will be held June 1 and 2, 1990, in St. Louis, Missouri. For further information, call (800) 325-9862 (national) or (314) 362-6893 (Missouri).

Wills Eye Hospital: 14th Annual Glaucoma Conference

The Wills Eye Hospital: 14th Annual Glaucoma Conference will be held June 1 and 2, 1990, in Philadelphia, Pennsylvania. For further information, write Department of CME, Wills Eye Hospital, 9th & Walnut Sts., Philadelphia, PA 19107.

Wilmer Institute: Third Annual Current Concepts in Ophthalmology

The Wilmer Institute: Third Annual Current Concepts in Ophthalmology course will be held Dec. 6–8, 1990, in Baltimore, Maryland. For further information, write Program Coordinator, Johns Hopkins Medical Institutions, Office of Continuing Education, Turner Building, 720 Rutland Ave., Baltimore, MD 21205; telephone (301) 955-2959.

Medical College of Wisconsin: Current Problems in Ophthalmology 1990

The Medical College of Wisconsin: Current Problems in Ophthalmology 1990 will be held June 8–10, 1990, in Kohler, Wisconsin. For further information, write Jeanne Dollar, Eye Institute, 8700 W. Wisconsin Ave., Milwaukee, WI 53226; telephone (414) 257-5353.

Hellenic Ophthalmological Society: 1990–1991 Officers

The Hellenic Ophthalmological Society 1990–1991 officers are as follows: S. Liarikos, president; S. Pollalis, vice president; N. Economopoulos, general secretary; A. Amariotakis, treasurer; E. Feretis, adjoint secretary; and A. Damanakis and N. Tsopelas, members.

Personals

P. K. Basu

Professor P. K. Basu presented the tenth annual Clement McCulloch lecture "My Research Experience at the University of Toronto Since 1955," on April 6, 1990.

Nancy J. Newman

Nancy J. Newman has been appointed assistant professor of neuro-ophthalmology in the Department of Ophthalmology at the Emory University School of Medicine, Atlanta, Georgia.

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AMERICAN JOURNAL OF OPHTHALMOLOGY

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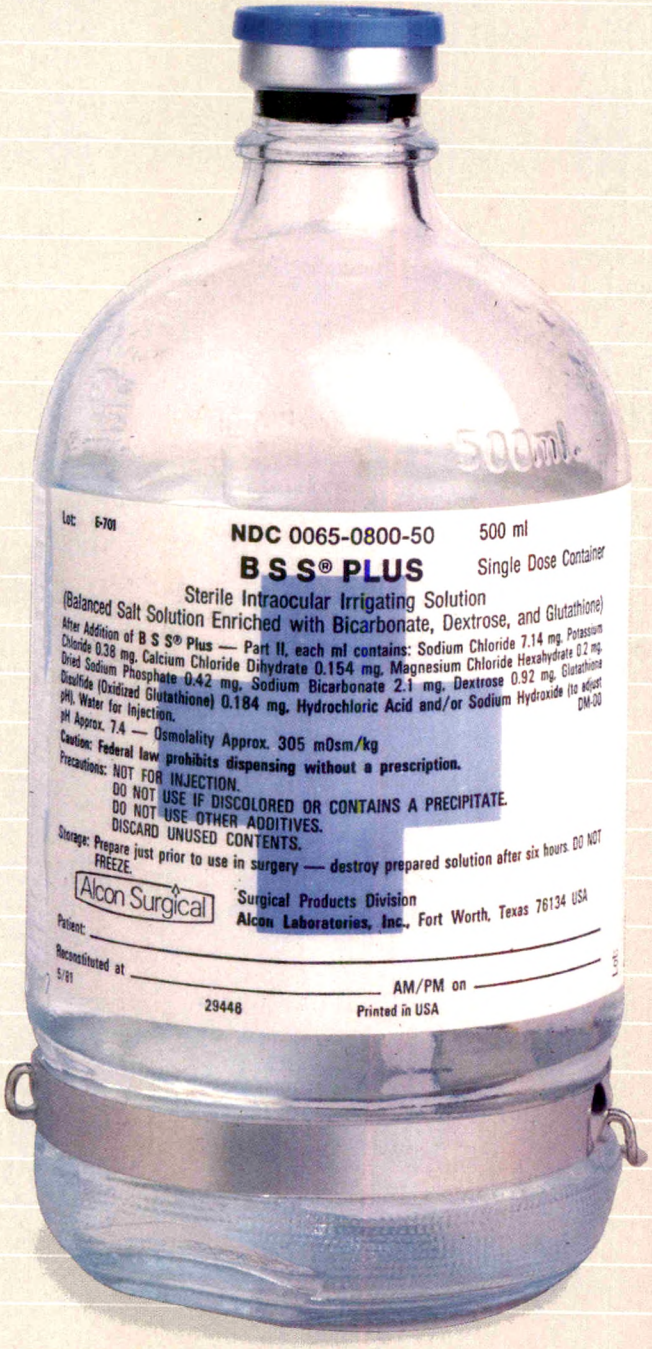

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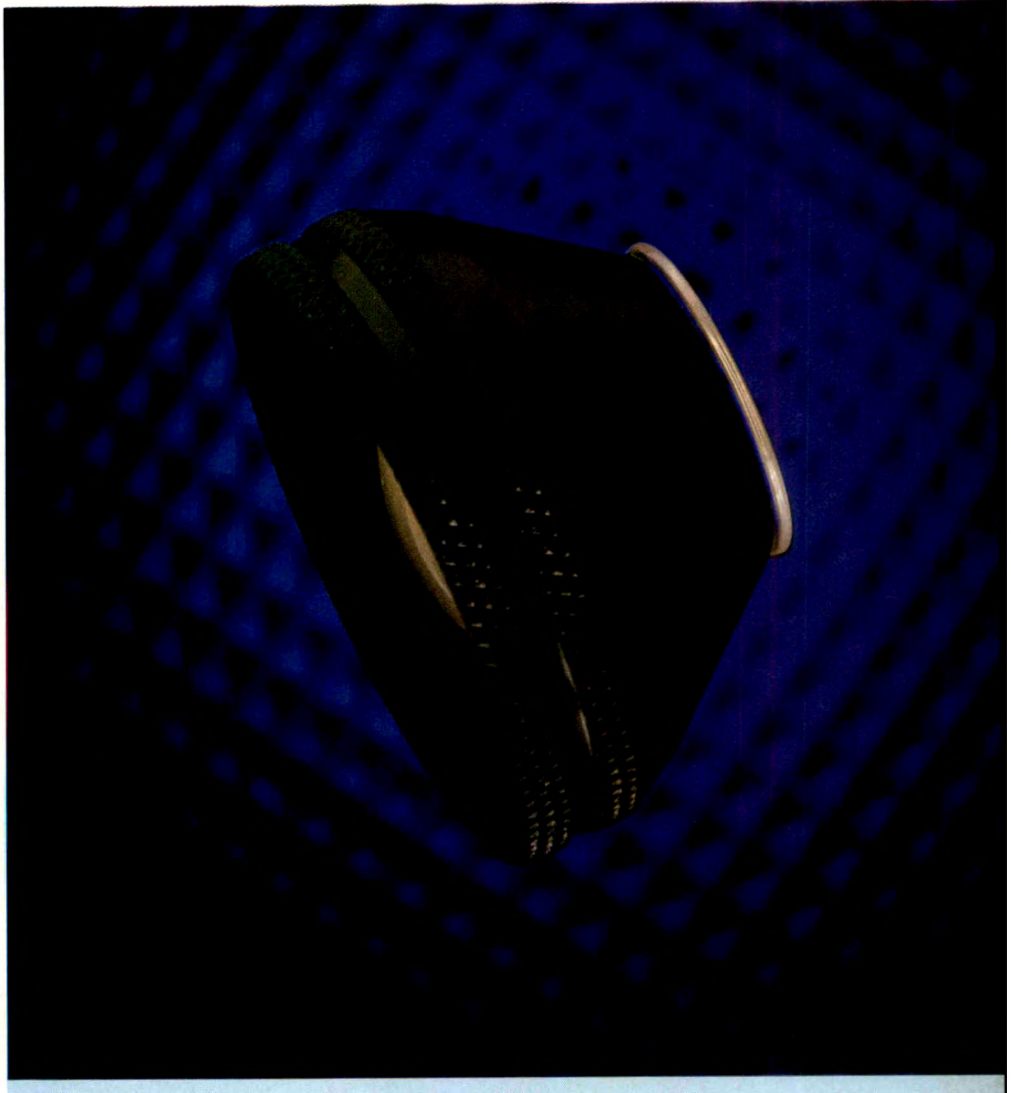

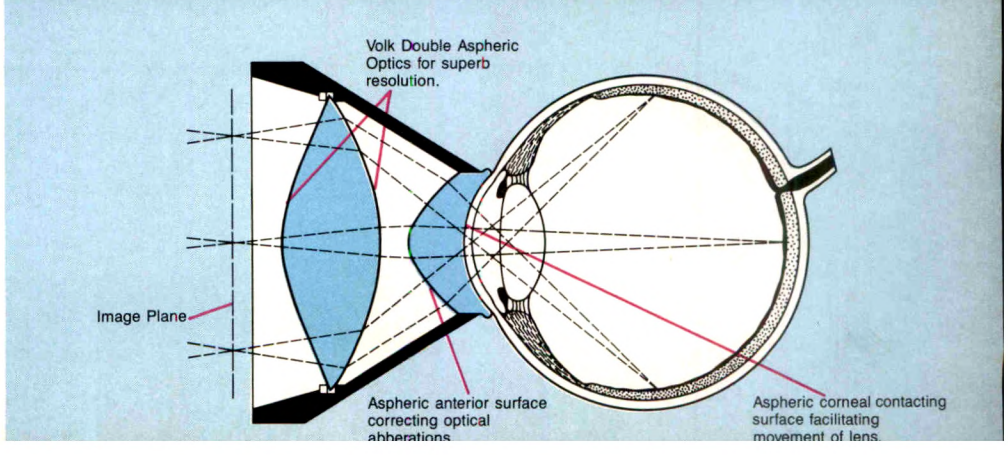

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AMERICAN JOURNAL OF OPHTHALMOLOGY®
VOLUME 109 NUMBER 5 MAY, 1990

Optic Disk Swelling With Peripheral Neuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS Syndrome)

James P. Bolling, M.D., and Paul W. Brazis, M.D.

We reviewed charts of patients seen at Mayo Clinic Rochester and Mayo Clinic Jacksonville to determine the importance and frequency of optic disk swelling in patients with peripheral neuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS syndrome). A computer search identified 148 patients who were classified as having a monoclonal gammopathy and peripheral neuropathy. A review of the 148 charts disclosed that 11 patients had POEMS syndrome. Eight of these 11 patients had optic disk swelling identified by an ophthalmologist. In all eight patients, optic disk swelling was either the initial sign or was present the first time we saw the patient. Optic disk swelling may be an early sign in POEMS syndrome.

PERIPHERAL NEUROPATHY, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS syndrome), or Crow-Fukase syndrome,[1] is a rare multisystem disorder, the cause of which is unknown. The acronym POEMS refers to the major features of this syndrome;[2] however, patients also typically have widespread edema, often with ascites and pleural effusions, lymphadenopathy, lethargy, weakness, shortness of breath, and optic disk swelling.[1,3-5]

Accepted for publication Feb. 9, 1990.
From the Section of Ophthalmology (Dr. Bolling), and the Department of Neurology (Dr. Brazis), Mayo Clinic Jacksonville, Jacksonville, Florida.
Reprint requests to James P. Bolling, M.D., Section of Ophthalmology, E-3B, Mayo Clinic Jacksonville, Jacksonville, FL 32224.

Since 1968, over 100 patients with this syndrome have been described, 63% to 68% of whom had optic disk swelling.[1,2] We reviewed charts to determine the frequency and importance of optic disk swelling as a sign in POEMS syndrome.

Material and Methods

A computer search of the records of over one million patients seen at Mayo Clinic Rochester and Mayo Clinic Jacksonville between January 1976 and September 1989 yielded 2,360 records of patients with multiple myeloma, plasmacytoma, or osteosclerotic myeloma. Of these charts, 148 were also coded for peripheral neuropathy. Of the 148 patients, 11 were identified as having POEMS syndrome, and eight of these had optic disk swelling. The course of these eight patients was similar, and optic disk swelling was an early finding in all eight patients (Table).

Case Reports

Case 1

A 57-year-old man developed headaches and obscurations of vision in early 1986 and had been followed up for two years by his ophthalmologist, who had made the diagnosis of papilledema (Fig. 1). A computed tomographic scan showed enlargement of the optic nerves, tomograms of the sella turcica and an electroencephalogram disclosed no abnormalities, and the

TABLE
CLINICAL DATA OF EIGHT PATIENTS WITH POEMS SYNDROME

PATIENT NO., AGE AT INITIAL EXAMINATION (YRS), SEX	INITIAL SIGN OR SYMPTOM	ABNORMAL PROTEIN LEVELS	X-RAY FINDINGS	ENDOCRINOPATHY	SKIN CHANGES	LUMBAR PUNCTURE FINDINGS
1, 57, M	Presumed papilledema	IgG lambda	Sclerosis L-2	Impotence, gynecomastia	Increased pigmentation	Increased protein level, normal pressure
2, 32, M	Lethargy	IgG lambda	Left ilium*	None	Increased pigmentation	Normal protein, normal pressure
3, 66, F	Neuropathy	IgG lambda	Sclerosis ilium*	None	Lentigo	Normal protein, normal pressure
4, 65, F	Weakness	IgA lambda	Right femur*	Diabetes	Increased pigmentation	Normal protein, normal pressure
5, 44, M	Weakness	IgA lambda	Sclerosis multiple	Gynecomastia	Increased pigmentation	Normal protein, normal pressure
6, 38, F	Neuropathy	IgG lambda	Sclerosis L-2	Virilization	Increased pigmentation, increased hair growth	Increased protein, normal pressure
7, 70, F	Neuropathy	IgA lambda	Sclerosis T-11, L-1	Diabetes	None	Increased protein, normal pressure
8, 61, M	Neuropathy	IgG lambda	Sclerosis T-9, 10, 11	None	Increased pigmentation	Increased protein, normal pressure

*Mixed sclerotic and lytic lesion.

patient had normal visual-evoked responses. An extensive medical evaluation in September 1986, in which the opening pressure on lumbar puncture was normal, was noncontributory. Since then, the patient developed progressive signs and symptoms of a sensorimotor peripheral neuropathy and had noted pretibial edema, whitening of the fingernails, increased skin pigmentation, and skin angiomas. Decreased hearing, impotence, and progressive shortness of breath had developed over the last year.

The patient underwent neurologic, endocrine, ophthalmologic, and oncologic examinations at Mayo Clinic Jacksonville in November 1988. The findings of peripheral sensorimotor polyneuropathy, optic disk swelling, deafness, organomegaly, pretibial edema, lymphadenopathy, hyperpigmentation of the skin, white fingernails, and gynecomastia were confirmed. On lumbar puncture, an opening pressure of 240 mm H_2O was obtained, with a spinal fluid protein level of 113.8 mg/dl (normal, 14 to 48 mg/dl). There was an IgG monoclonal protein spike in the serum, and results of urine immunoelectrophoresis were positive for a monoclonal lambda fragment. Magnetic resonance imaging of the brain disclosed no abnormalities. Plain films of the lumbar spine showed an osteosclerotic lesion in the vertebral body of the L-1 vertebra, and magnetic resonance imaging confirmed this abnormality (Fig. 2). Results of a lymph node biopsy were consistent with Castleman's disease.

The diagnosis of POEMS syndrome was made, and the osteosclerotic lesion in the L-1 vertebra was presumed to be a plasmacytoma. The patient underwent external beam irradiation to the lesion and had some remission of his neuropathy, hyperpigmentation, and fingernail changes. The optic disk swelling has persisted for nine months.

Case 2

A 32-year-old man complained of lethargy in April 1986 and had a platelet count of 731,000/μl. He developed a peripheral neuropathy, and during examination for this, he was noted to have lymph node histopathologic characteristics consistent with Castleman's disease. In March 1986, bilateral optic disk swelling was diagnosed, and the patient was admitted to the hospital for further examination. A computed tomographic scan of the brain disclosed no abnormalities, and the spinal fluid was normal. The patient developed bilateral pleural effusion and diffuse anasarca. A computed tomographic scan of the abdomen showed an enlarged liver and enlarged retroperitoneal and mesenteric lymph nodes.

In August 1988, the patient was referred to

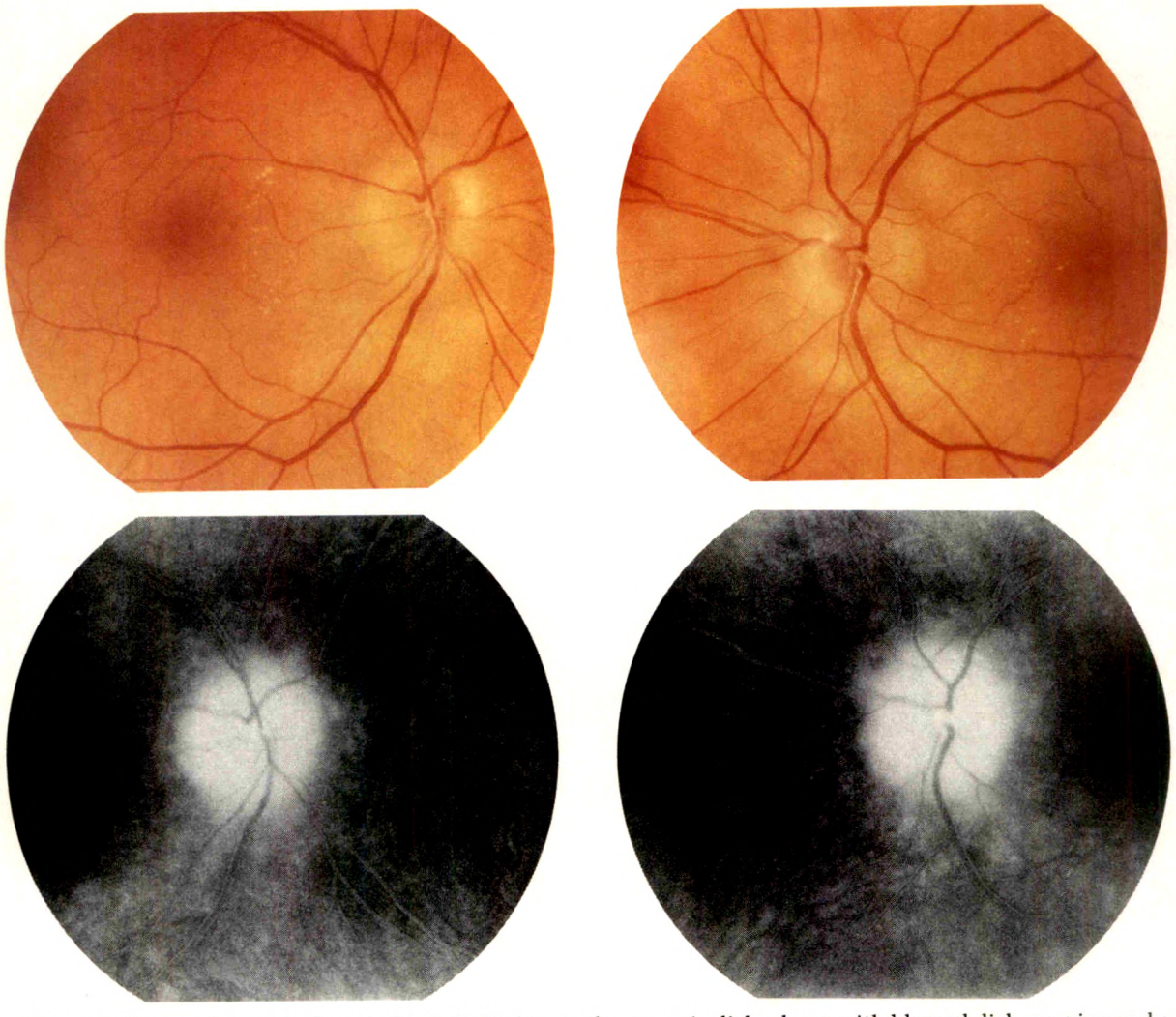

Fig. 1 (Bolling and Brazis). Case 1. Top left, Right eye shows optic disk edema with blurred disk margins and a few exudates between the fovea and the disk. Top right, Left eye shows blurred disk margins and exudates temporal to the optic nerve. Bottom left, Fluorescein angiogram of the right eye (late phase) shows disk edema. Bottom right, Fluorescein angiogram, left eye (late phase) shows edema.

the Mayo Clinic Rochester for further examination. The previous findings were confirmed. Additionally, hyperpigmentation of the skin was noted. A lymph node biopsy specimen confirmed Castleman's disease, and a mixed sclerotic and lytic lesion was noted in the patient's ilium on plain films. Bone marrow biopsy of this lesion, attempted under computed tomographic guidance, was unsuccessful. Results of serum and urine immunoelectrophoresis were normal. Ophthalmologic examination disclosed a visual acuity of 20/20 in both eyes with bilateral optic disk swelling. Visual field examinations showed enlarged blind spots (Fig. 3).

The patient was seen again in March 1989. The blind spots were larger, and a nasal step was present in each eye (Fig. 4). Visual acuity remained 20/20 in both eyes. A presumptive diagnosis of malignant plasma cell infiltration of the left ilium was made despite failure to detect an abnormal serum protein level. Radiation to the lesion was advised. The patient returned to his local physician and has not returned to us for follow-up.

Case 3

A 66-year-old woman developed a progressive peripheral neuropathy in the spring of 1978. A cause was not found, and in April 1979

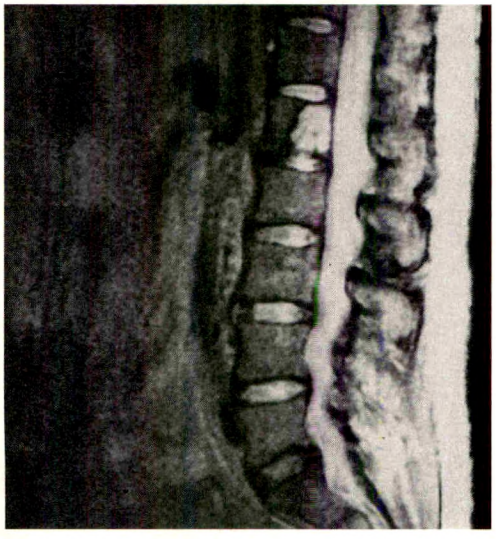

Fig. 2 (Bolling and Brazis). Case 1. A magnetic resonance scan (T2) shows a hyperintense focus in the posterior aspect of the L-1 vertebral body.

she was referred to Mayo Clinic Rochester. An ophthalmologic examination disclosed blurred disk margins nasally and a peripapillary hemorrhage in the left eye. The liver was enlarged. An irregular sclerotic lesion was present in the left ilium on plain films. A biopsy of the lesion was taken, and the diagnosis of plasmacytoma was made. A monoclonal serum protein level of 1.69 g/dl was found, and immunoelectrophoresis showed an IgG lambda fragment in the serum. A biopsy of a pigmented lesion on the right shoulder was taken and found to be a lentigo maligna. The patient was referred to her local physician for radiation treatment to the left ilium.

The patient was seen again in August 1979. Her neuropathy had improved. Results of immunoelectrophoresis showed no evidence of monoclonal gammopathy. Disk swelling had resolved, and some pigment was seen around the left disk.

Case 4

A 65-year-old woman had a history of diabetes mellitus and complained of progressive weakness in her limbs since early 1977. In February 1978, peripheral neuropathy was diagnosed. In May 1979, she was noted to have optic disk swelling, which was unchanged after a short course of corticosteroids.

The patient was referred to Mayo Clinic Rochester where her examination confirmed the finding of peripheral neuropathy. Visual acuity was 20/25 in both eyes, and both optic disks were swollen. An IgA lambda monoclonal gammopathy was discovered, and a rectal biopsy specimen disclosed no amyloidosis. Review of x-rays taken elsewhere showed a mixed lytic and sclerotic lesion in the right femur. A biopsy

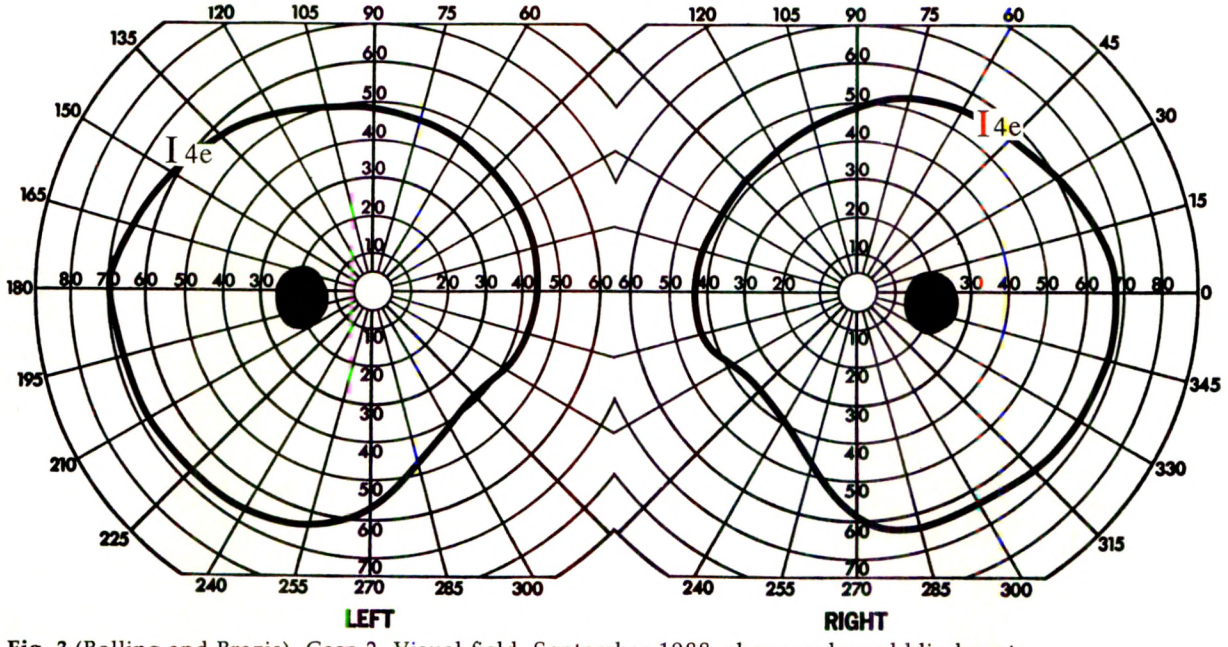

Fig. 3 (Bolling and Brazis). Case 2. Visual field, September 1988, shows enlarged blind spots.

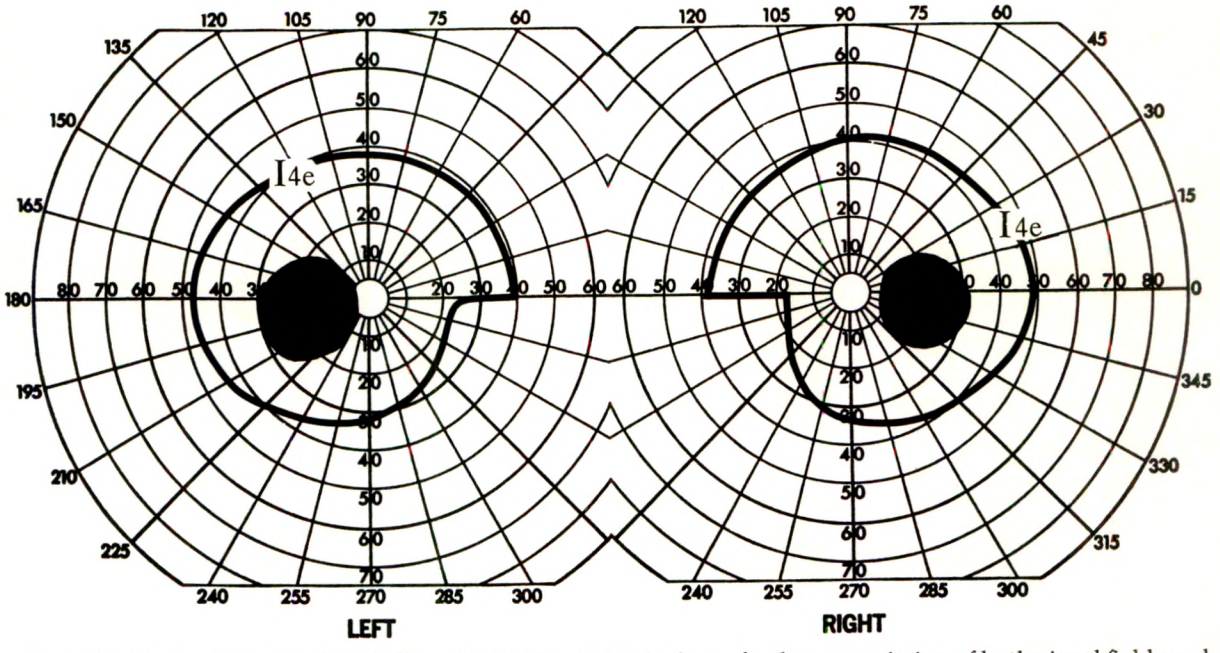

Fig. 4 (Bolling and Brazis). Case 2. Visual field, March 1989, shows further constriction of both visual fields and further enlargement of the blind spots and the nasal step in both eyes.

specimen of this lesion showed characteristics that were consistent with myeloma. The diagnosis of POEMS syndrome was made, and the patient was referred to her internist. Arrangements were made for external beam radiation to the right femur. The patient was lost to follow-up.

Case 5

A 44-year-old man had been unable to work for two weeks because of leg weakness, which was progressive over four months and attributed to diabetes. The patient was seen in July 1983; his skin was deeply pigmented, and he had axillary lymphadenopathy, gynecomastia, and an enlarged liver. There were no reflexes at the knees or ankles, and he could not walk on his heels or toes. Visual acuity was 20/20 in both eyes, and intraocular pressure was 15 mm Hg in both eyes. The patient had 1 to 2 diopters of optic disk swelling bilaterally.

The patient had multiple small sclerotic bone lesions noted on plain films. A biopsy specimen of the right clavicle showed myeloma. Immunologic stains were positive for lambda protein. A biopsy specimen of a left inguinal lymph node showed reactive hyperplasia. The patient was treated with prednisone and melphalan. He suffered a stroke in August 1983, and he was hospitalized again in October 1983 for a feeding gastrostomy. He was eventually transferred to his local hospital and died in September 1984. No autopsy was performed.

Case 6

A 38-year-old woman reported a diagnosis of "atypical Guillain-Barre syndrome" made in October 1982 with weakness in the arms and legs associated with a spinal fluid protein level greater than 200 mg/dl. She also reported having a positive VDRL and negative fluorescent treponemal antibody absorption test results. She requested another opinion about her progressive weakness.

When we first examined the patient in December 1984, she had darkening of the skin, axillary lymphadenopathy, and sensorimotor peripheral neuropathy. On ophthalmologic examination, the visual acuity was 20/20 in both eyes. The optic disks were swollen, and there was a retinal hemorrhage inferior to the right disk. Visual field examination showed an enlarged blind spot in both eyes.

The hemoglobin level was 16 g/dl, the white blood cell count was 16,100/μl, and the platelet count was 977,000/μl. Immunoelectrophoresis showed a monoclonal IgG lambda protein in the serum. The spinal fluid protein level was 81 with a normal opening pressure. A computed tomographic scan showed a sclerotic

lesion in the anterior portion of the L-2 vertebra, which was diagnosed as multiple myeloma on open biopsy. The patient was referred back to her local radiotherapist for radiation to the L-2 vertebra and was lost to follow-up.

Case 7

A 70-year-old woman developed a mixed sensorimotor peripheral neuropathy in 1982. She had insulin-dependent diabetes mellitus for approximately three years and had noted transient obscurations of vision for the past year.

The patient was referred to the Mayo Clinic Rochester in March 1983. Visual acuity was 20/20 in both eyes, and intraocular pressure was normal. Both optic disks were swollen, and the liver was enlarged. An increased spinal fluid protein level and a normal opening pressure were noted on lumbar puncture. Serum immunoelectrophoresis identified a monoclonal IgG lambda spike. Osteosclerotic lesions were noted in the vertebral bodies of L-1 and T-11 on plain films. The patient was lost to follow-up.

Case 8

A 61-year-old man complained of increasing pain and numbness in his feet, legs, and later his hands starting in March 1979. The patient had developed weakness in his arms and legs, and he was referred for evaluation of his peripheral neuropathy.

Physical examination disclosed increased skin pigmentation and increase in hair growth on the patient's arms and legs. He had a profound peripheral neuropathy with no reflexes in the lower extremities, marked weakness, and decreased sensation to all sensory modalities. Ophthalmologic examination disclosed visual acuity of 20/30 in both eyes and bilateral optic disk swelling.

Electromyogram confirmed a severe peripheral neuropathy, and spinal fluid examination showed an increased protein level of 140 mg/dl. Plain films of the thoracic spine showed a lesion involving the vertebral body of T-10 with a pathologic compression fracture. A radioactive bone scan showed increased radioisotope tracer uptake involving T-9 and T-10 and the right side of T-11. The adjoining portion of the ninth right rib also showed increased uptake, and a biopsy specimen was taken. Histopathologic examination of this lesion showed a poorly differentiated small cell malignant neoplasm, and immunohistochemical stains disclosed the presence of lambda light chains within the tumor. The final diagnosis was lymphoma with plasma cell differentiation.

Discussion

The POEMS syndrome is a multisystem disorder found in patients with monoclonal gammopathy. Monoclonal gammopathy refers to a spectrum of plasma cell abnormalities, including benign proliferations, lesions of undetermined significance, and obvious neoplasms. The osteosclerotic form of multiple myeloma seems to be strongly associated with POEMS syndrome. Although the osteosclerotic variant accounts for only 1% to 2% of cases of multiple myeloma, 85% of patients with POEMS syndrome have either osteosclerotic or mixed osteosclerotic and lytic forms.[6] As shown by this series, these tumors are frequently isolated and often occur in the spine or pelvis. The monoclonal protein produced has the characteristics of an IgG or IgA containing almost exclusively lambda light chains (in contrast to a 2:1 ratio for kappa:lambda light chains found in multiple myeloma in general).[7]

Peripheral neuropathy is a major component of POEMS syndrome and is found in virtually all affected patients.[1,2] Otherwise, peripheral neuropathy is uncommon in multiple myeloma, occurring in only 3% to 5% of patients.[8,9] The neuropathy is usually progressive, predominantly of the motor or sensorimotor type,[4] and relatively homogeneous[10] (in contrast to the heterogeneous pattern seen with multiple myeloma). Sural nerve biopsy specimens show either pure axonal degeneration or both axonal degeneration and segmental demyelination.[1,2] Symptoms usually begin in the legs and progress to the arms.

Endocrine abnormalities are found in 60% to 80% of patients.[1,2] It was reported that the IgG lambda protein in one patient with POEMS syndrome reacted with pituitary gland tissue; it was suggested that the binding of antibodies to the pituitary gland could produce a secondary endocrinopathy.[11] Primary gonadal failure may cause gynecomastia and impotence or amenorrhea. Glucose intolerance or obvious diabetes mellitus is found in 28% to 48% of patients.[2] Hypothyroidism, hyperthyroidism, and adrenal insufficiency have been reported.

The most common skin change seen in patients with POEMS syndrome is diffuse hyper-

pigmentation, which has been noted in 93% to 98% of patients.[1,2] Apparent thickening of the skin and hypertrichosis also occur.[12-15]

Hepatomegaly is the most common organomegaly seen in patients with POEMS syndrome (82% of patients).[1,2] Splenomegaly occurs in 39% of patients, and lymphadenopathy occurs in 65% of patients.[1] Lymph nodes in POEMS syndrome patients often have a pathologic appearance with proliferating capillaries among sheaths of mature plasma cells. This histopathologic finding is indicative of Castleman's disease[16] and was seen in three of our patients. Other less common clinical features of POEMS syndrome include peripheral edema, pleural effusions, finger clubbing, white fingernails, verrucous angiomas, ascites, fever, and pupillary light-near dissociation.[2,4]

Bardwick and associates[2] found that 68% of patients described in published reports had papilledema. Nakanishi and associates[1] reviewed 102 cases in Japan and found that 63% of these patients had papilledema. Of the patients described in published reports, 58% had papilledema as determined in a more recent study by Viard and associates.[15] In our series, eight of 11 patients with POEMS syndrome had disk swelling. All eight of these patients had been seen by an ophthalmologist; the three patients who did not have disk swelling were not seen by an ophthalmologist.

The cause of optic disk swelling is unclear. It may occur in the absence of increased intracranial pressure or increased levels of spinal fluid protein.[17] One patient with POEMS syndrome had orbital pain and a computed tomographic scan that showed diffuse edema of the posterior orbital contents bilaterally; the orbital pain and swelling resolved with systemic corticosteroids.[18] Trentham, Masi, and Marker[17] demonstrated small vessel abnormalities in POEMS syndrome patients, which suggests that the disease is secondary to a vascular disease or some type of occluding microvascular disorder. It has also been suggested that the monoclonal protein, or some other factor secreted by the tumor, could cause the multisystem disease (including optic disk swelling). Bardwick and associates[2] could not, though, demonstrate any antineuronal or antiglial activity to the monoclonal protein, and, indeed, in some patients, no monoclonal protein may be found. Recently, Gittinger[19] reported ocular involvement by Castleman's disease. The patient had optic disk swelling and developed choroidal infiltration and nonrhegmatogenous retinal detachment. These abnormalities resolved with radiation. Possibly, optic disk swelling in patients with POEMS syndrome is caused by infiltration of the optic nerve or nerve sheath with lymphoid cells. Finally, as noted above, specific antibody activity against a pituitary tumor has been shown in one case of POEMS syndrome, which suggests that the disease may be secondary to an endocrinopathy.[11]

In all eight of our patients, optic disk swelling was present at the time of referral to a tertiary care center. In most cases, no additional laboratory tests were necessary to support the diagnosis of POEMS syndrome. That none of the eight patients had a unifying diagnosis that explained their symptoms shows that this disease is not often recognized by ophthalmologists. It is also evident that optic disk swelling, when present, can be an early sign of POEMS syndrome. The patients described herein had a clinical course similar to papilledema associated with increased intracranial pressure and had transient obscuration of vision, good visual acuity, enlarged blind spots, and progressive constriction of the visual field.

In patients with single lesions, radiation of localized sclerotic lesions or surgical extirpation, occasionally combined with chemotherapy (such as melphalan), may improve the patient's condition or induce complete remission of the syndrome in some patients,[1,13] and even resolve the disk swelling (as in Case 3). In patients with multiple osteosclerotic lesions, chemotherapy may be beneficial, but the response is usually poor compared to that in patients with single plasmacytomas.

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OPHTHALMIC MINIATURE

"I used to worry about you, Zoyd, but I see I can rest easy now the Vaseline of youth has been cleared from your life's lens by the mild detergent solution of time, in its passing . . ."

Thomas Pynchon, *Vineland*
Boston, Little, Brown and Company, 1990

Ciliary Vasoconstriction After Topical Adrenergic Drugs

E. Michael Van Buskirk, M.D., David R. Bacon, B.S., and Wolf H. Fahrenbach, Ph.D.

Rabbits underwent the single-dose or long-term therapeutic administration of the adrenergic drugs phenylephrine hydrochloride, timolol maleate, and betaxolol hydrochloride. After a single dose, all three drugs caused substantial, localized constriction in the arterioles that supply the ciliary processes but did not affect the downstream bore of the same vessels. After seven weeks of a daily dose, tolerance reduced the response to betaxolol to insignificant levels and that to phenylephrine substantially, whereas timolol maleate continued to produce identical levels of vasoconstriction to those seen with single-dose administration. In addition to the consequent lowering of perfusion of the ciliary processes and presumptive impact on aqueous humor production, vasoconstriction also reinforces concerns about impaired vascular perfusion of eyes undergoing long-term ocular therapy.

ADRENERGIC DRUGS such as phenylephrine, epinephrine, and a variety of β-antagonists have many applications in ocular therapy, usually for properties other than their vasomotor activity. Vasoconstriction can be induced in ocular vessels by agonist drugs such as phenylephrine or epinephrine, or, indirectly, by blockade of β_2-receptors with β-adrenergic antagonists, such as timolol maleate, levobunolol, or betaxolol. The last decade has seen the increasing application of adrenergic compounds, both agonists and β-antagonists, to glaucoma therapy. The mechanism by which these agents reduce intraocular pressure is not entirely understood, but recent studies suggest that they act primarily through adrenergic receptors in the target tissue, the ciliary epithelium for β-antagonists, and the trabecular meshwork for epinephrine.[1-6]

Many questions, however, remain unanswered; for example, a selective, primarily β_1-antagonist, betaxolol, reduces intraocular pressure comparably to nonselective β-blockers, but studies in vertebrate eyes, including human eyes, have shown primarily β_2-receptors in the ciliary body.[7] The doses of timolol maleate required to reduce intraocular pressure in rabbits are considerably higher than those needed to block the effects of β-agonists,[7] which suggests that some other hypotensive mechanisms may also occur. Although a variety of mechanisms are possible, these adrenergic drugs also have potent vasomotor effects that could contribute to their hypotensive activity or cause local ischemic, toxic effects on the anterior segment of the eye.

We previously used microvascular corrosion casting to examine and characterize the microvasculature in the eyes of primates, rabbits, and other mammals.[8-12] In these studies, we described constrictor cuffs in arterioles supplying the ciliary process arterioles in monkeys, rats, and rabbits that provide an anatomic basis for regional alterations in ciliary blood flow.[13] Macri and Cevario[14] studied aqueous humor and blood flow dynamics in the cat eye and concluded that various pharmacologic agents "decrease aqueous humor formation by producing vasoconstriction of afferent ciliary-process vessels to decrease intraluminal pressure and consequently to decrease aqueous humor ultrafiltration." They postulated the existence of vascular sphincters in a location at both the arteriolar and venous sides of the ciliary processes.

Our studies tested the hypothesis that adrenergic drugs administered as eyedrops could alter vasomotor activity in uveal vessels. We manipulated arteriolar vascular constrictor cuffs in the ciliary vasculature of the rabbit by means of three commonly used adrenergic

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drugs: an α-agonist, phenylephrine; a nonselective β_1- and β_2-antagonist, timolol maleate; and a cardioselective, primarily β_1-antagonist, betaxolol.

Material and Methods

Adult, normal, nonpigmented rabbits received one drop of the test drug centrally on the cornea of the left eye approximately one hour before microvascular casting. The three drugs tested were phenylephrine hydrochloride 2.5% (four eyes), timolol maleate 0.5% (two eyes), and betaxolol hydrochloride 0.5% (two eyes). Each eye was compared to the fellow, untreated eye, which in no case gave evidence of a consensual response, and each eye was compared to a pool of untreated control eyes (15 eyes).

Seven other rabbits underwent unilateral long-term therapy (one drop daily) with one of three drugs for 50 days. Three rabbits were treated with phenylephrine hydrochloride, two rabbits were treated with timolol maleate, and two rabbits were treated with betaxolol hydrochloride. Drug habituation was tested by statistical comparison of these eyes to those exposed to a single dose of the drug.

Castings of the ocular vasculature were obtained under controlled physiologic conditions as described previously.[13] In this technique, it is important to maintain the physiologic homeostasis of the animal, to use a low-viscosity plastic (11 centipoise) at physiologic temperature (37 C) and injection pressure (100 to 120 mm Hg), and to maintain that injection pressure until the plastic sets, which is about 15 minutes. Two hours after injection, the eyes were enucleated, stored overnight in warm formalin to complete the polymerization, and corroded in potassium hydroxide. The clean castings were rinsed in running water and air dried.

The anterior segment of the casting was mounted on a large stub, and the major arterial circle of the iris was exposed for its entire circumference by careful dissection of the overlying ciliary muscle capillaries. The casting was sputter-coated with 20 to 30 nm of gold and examined with a scanning electron microscope.

Each anterior and posterior radial arteriole was measured at the constricted zone near the branching point from the major circle of the iris and at a reference point downstream beyond the constriction, usually at a distance of 50 to 100 μm (Fig. 1). These measurements were grouped as absolute diameters at the constricted and downstream sites in the experimental and control eyes, and as a mean level of constriction for each eye (constriction [%] = con-

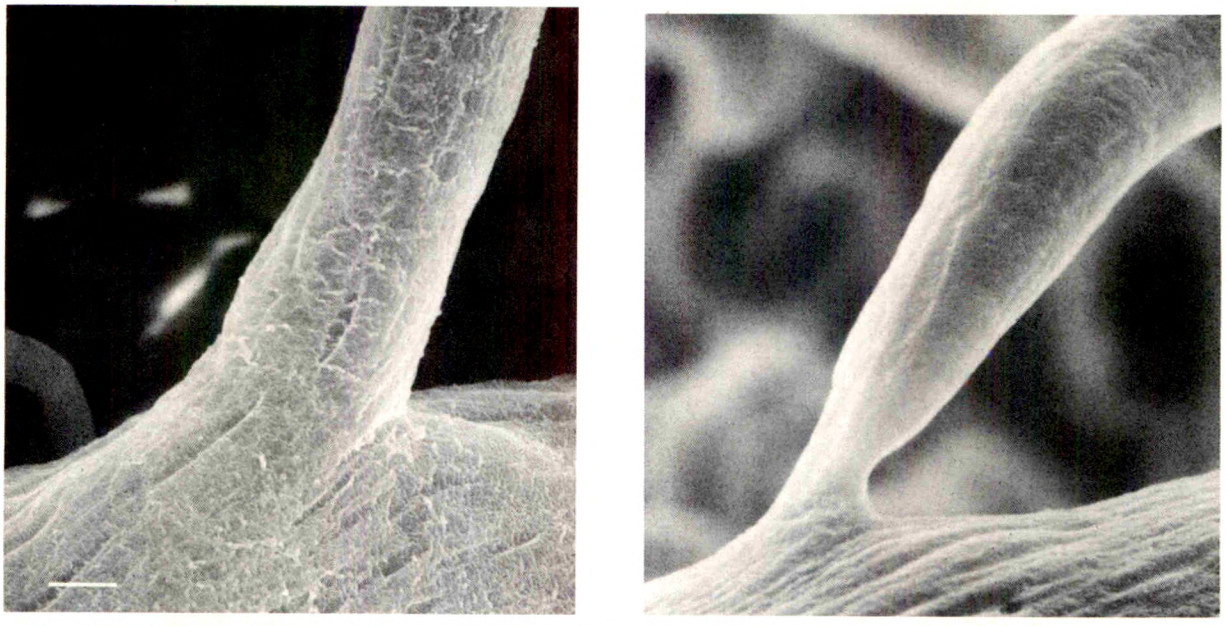

Fig. 1 (Van Buskirk, Bacon, and Fahrenbach). Left, Branching point of a radial arteriole from the major arterial circle in a control animal. Right, Constricted branching point of a radial arteriole after the administration of phenylephrine (×900). Bar = 10 μm.

stricted diameter/downstream diameter × 100 − 100). Because of the large variation in diameters of radial arterioles as well as the statistical variability of individual responses, we accumulated a large control group of measurements, to which the results from experimental eyes could be compared. This global control group also served as a check on the normality of untreated fellow eyes in animals in which a systemic or consensual effect was suspected. In all cases, one eye of any experimental animal served as the paired control. Anterior and posterior radial arterioles responded in a statistically indistinguishable manner to the drugs and were, therefore, grouped together. In all cases, stated values for constriction refer to the mean value of all the vessels of one or more eyes. Descriptive statistics, Student's *t*-tests, and graphing were done with a computer.

Results

Under conditions of a physiologically controlled casting technique, the downstream diameters of the radial arterioles were consistent. In the control group (459 vessels), the mean arteriolar downstream diameter was 47.4 μm ± 0.8 (S.E.M.). These control vessels exhibited a 15.2% (±0.7) constriction at the cuff near the branching point from the major arterial circle.

After exposure to the various adrenergic drugs in the single-dose group, the downstream diameters remained constant or even dilated, with means of 48.6 μm (± 1.5) after phenylephrine (170 vessels); 46.0 μm (± 1.9) after timolol maleate (87 vessels); and 48.3 μm (± 1.5) after betaxolol (98 vessels). None of the downstream diameters differed significantly from those of the paired control eyes (P = .73 for phenylephrine, P = .78 for timolol maleate, and P = .92 for betaxolol).

In contrast to the downstream diameters, however, the arteriolar cuff of these eyes showed marked constriction after single-dose drug treatment. The phenylephrine-treated eyes had a mean arteriolar constriction of 32.0% (±1.6), the timolol-treated eyes had a mean constriction of 22.9% (±1.5), and 30.0% (±1.6) narrowing was found after the administration of betaxolol. The constriction of the arteriolar cuff after the administration of these three drugs was highly significant (P = .0001) compared to that of the controls (Fig. 2).

In contrast to the eyes that received only one dose of the drug, only those in the long-term group that received timolol maleate and phenylephrine continued to manifest vasoconstriction after about seven weeks of therapy. The arterioles in the timolol maleate-treated eyes showed 21.5% (±1.4) mean constriction after long-term therapy compared to 22.9% after one dose, a difference which was not statistically significant (P = .51). In contrast, eyes treated with phenylephrine or betaxolol showed much less focal vasoconstriction (20.0% [±2.0] and 15.8% [±1.7], respectively) after long-term therapy compared to 32.0% and 30.0%, respectively, after single-dose administration (Fig. 2). After long-term therapy, the vasoconstriction produced by betaxolol did not deviate significantly from the level found in

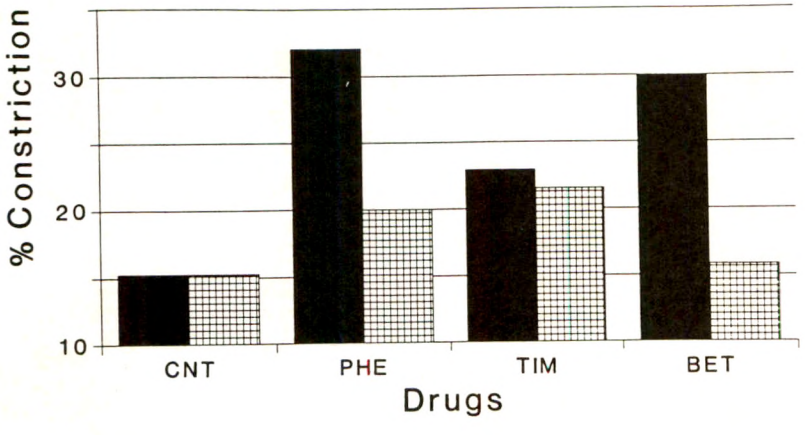

Fig. 2 (Van Buskirk, Bacon, and Fahrenbach). Percent constriction of radial arterioles after single-dose (solid bars) and long-term (shaded bars) drug therapy is shown. CNT indicates control; PHE, phenylephrine; TIM, timolol maleate; and BET, betaxolol.

untreated control eyes (P = .99), and the level for phenylephrine barely reached the level of significance (P = .032) (Figs. 2 and 3).

Discussion

Our previous studies demonstrated the presence of focal vasoconstriction in the arterioles that supply the ciliary processes in rat, rabbit, and monkey eyes[13,15] similar to that hypothesized in the cat by Macri and Cevario.[14] Originally, we could not rule out vasoconstrictor activity of the methacrylate itself, and we further suspected agonal vasoconstriction by autonomic stimulation in response to the stress of the procedure. However, with the refinement of our injection technique, including the maintenance of optimal physiologic conditions up to the moment of injection, we observed only minimal vasoconstriction in the control condition.[13] Any vasoconstriction beyond this minimal amount had to be experimentally produced either by an induced release of endogenous neurohormones or from exogenously administered pharmacologic agents. All three drugs selectively contract the precapillary arteriolar sphincter, but do not produce diffuse narrowing of the downstream arterioles. Downstream narrowing of the ciliary arterioles and capillaries has been reported by Funk[16] and Funk and Rohen,[17-21] but our experiments have shown that this effect results from the release of injection pressure before the plastic has hardened.[13] The resultant drop in internal pressure combined with residual tone of the vessels and tissue pressure combine to cause the vessels to collapse.

Our study demonstrated focal vasoconstriction in the ciliary microvasculature of the rabbit eye after single-dose topical ocular exposure to an adrenergic agonist, phenylephrine; a nonselective β-adrenergic antagonist, timolol maleate; and a β_1-selective antagonist, betaxolol. It also showed that whereas the vasoconstriction persists after prolonged exposure to the nonselective β-blockers, it diminishes to statistically insignificant levels after long-term exposure to the selective β-blocker betaxolol. Long-term phenylephrine exposure also produced a diminution of the response, but some vasoconstriction persisted.

Pharmacologically, these results confirm that α-adrenergic stimulation with phenylephrine and β-adrenergic antagonism, presumably through the blockade of β_2-receptors, produces focal vasoconstriction in peripheral vessels. Although betaxolol is primarily a β_1-antagonist, apparently it possesses enough β_2-blocking activity in a single dose to block widely distributed β_2-receptors in the ciliary body.[22] Furthermore, long-term administration apparently causes sufficient down-regulation of receptor-blocking activity, thus eliminating any vasoconstriction after long-term betaxolol therapy.

These data suggest the likelihood that such pharmacologic vasoconstriction, demonstrated in the rabbit eye, could also occur in the human eye. Obvious differences exist between the rabbit and primate eye, such as the response of the blood-aqueous barrier to injury,[23] or the minimal effect of timolol maleate on intraocular pressure in rabbits.[24] Nevertheless, the ciliary process microvasculature of both rabbit and primate has important features in common that make the rabbit a suitable model to investigate vasoconstrictive activity of topical drugs.[11,12] Although the rabbit eye does not exhibit as dramatic an ocular hypotensive response to β-blockers as do some mammalian eyes, both betaxolol and timolol maleate readily permeate the cornea and enter the anterior chamber. Of ten mammalian species studied, only the primate eye and rabbit eye have a dual arteriolar supply to each ciliary process. Both species have a precapillary constrictor cuff in the wall of the radial arterioles just as they branch from the major arterial circle of the iris.[8,11,19,20]

Our study demonstrates an approximate 21.5% reduction in arteriolar diameter at the constrictor site after the long-term administration of timolol maleate and 20% after the long-term administration of phenylephrine. This focal constriction would be expected to impede perfusion of the ciliary processes as well as of the choroid, because there are no unaffected arterioles branching from the major arterial circle. At most, some shunting through posterior arterioles can be postulated; about 50% of these arterioles have direct connections to the choriocapillaris, although they are also subject to drug-induced stenosis. The net ciliary blood flow can be expected to diminish in proportion to the fourth power of the radius of the constriction and thus be profoundly reduced during the intense stenosis that is frequently observed. Such vasoconstriction in the primate eye could have a more profound effect on ciliary process perfusion than in the rabbit. The ciliary microvascular anatomy in the primate suggests that the primate has a greater capacity to shunt

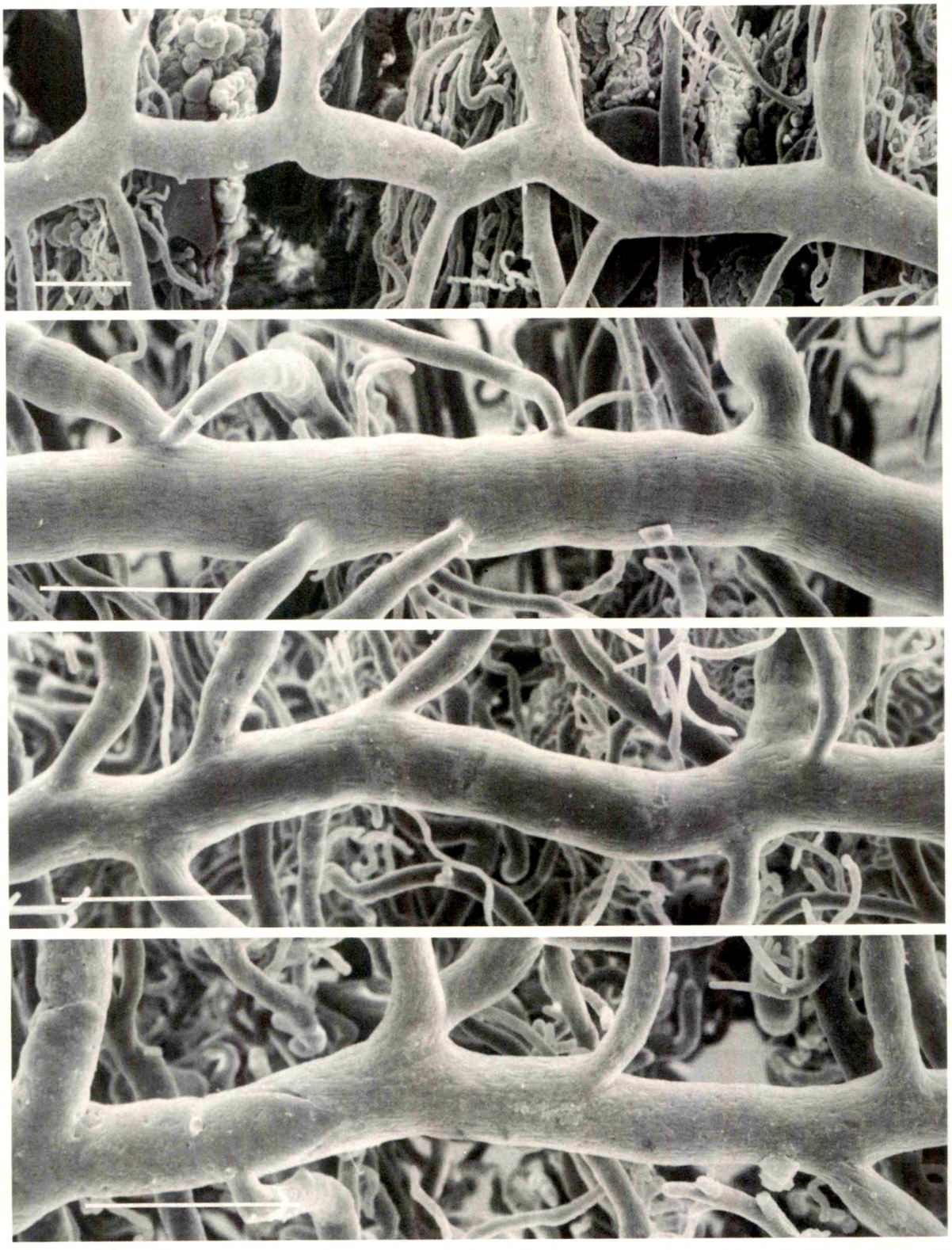

Fig. 3 (Van Buskirk, Bacon, and Fahrenbach). Short segments of the major arterial circle with several radial arterioles after various drug regimens. Top, Control (× 80); second from top, long-term phenylephrine (× 150); second from bottom, long-term timolol maleate (× 160); bottom, long-term betaxolol (× 180). Bars = 200 μm.

blood selectively away from the ciliary process tips and toward the choroid, because only the anterior ciliary process arterioles exhibited the focal vasoconstriction.[9]

Although both β-blockers studied reduce aqueous humor formation in the primate, none of the drugs tested consistently reduces aqueous humor formation in the rabbit.[7,25] Thus, the direct effect of the manifest vasoconstriction and concomitant reduction of ciliary process blood flow on aqueous humor dynamics is not known. The difference between timolol maleate and betaxolol in reducing intraocular pressure and aqueous flow may be a consequence of the effects of long-term drug administration. Timolol maleate generates no tolerance, whereas the stenosis generated by the single-dose administration of betaxolol no longer occurred after long-term therapy.

Even if these vascular changes do not alter aqueous humor formation, such focal vasoconstriction could produce some harmful effects, especially if the vasoconstriction occurs in the posterior segment to a comparable degree as we have observed in the ciliary vasculature. Some clinicians have recently postulated that topical β-blockers, despite their intraocular pressure lowering effect, may exacerbate glaucomatous optic disk damage by inciting vasoconstriction in the vessels that supply the optic nerve.[26,27] Our study has not yet addressed the effects of drugs on the optic disk vasculature, but it supports this concern by demonstrating prolonged ocular vasoconstriction caused by long-term, topical administration of the nonselective β-adrenergic antagonist, timolol maleate.[28]

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OPHTHALMIC MINIATURE

Spiridon downed a whole glass, and the "bastard-in-law" drank down the rest of it. Fortunately, his sons were not there, too, or they would have had a glass also. When he awoke after midday, Spiridon was frightened because it was dark so early, and he stuck his head out the window. But it was not very light there either, and he couldn't understand for a long time why the upper half of the guard post and the American headquarters across the street didn't exist, but the lower did. He wanted to hide his misfortunes from Marfa, but by evening the mantle of blindness had covered his eyes completely.

Aleksandr I. Solzhenitsyn, *The First Circle*, trans. by Thomas P. Whitney New York, Harper & Row, 1968, p. 398

Pigmentary Glaucoma in the Black Population

H. Christopher Semple, M.D., and Stuart F. Ball, M.D.

The pigment dispersion syndrome is associated with a secondary open-angle glaucoma most commonly found in young, myopic, white males. We studied 20 cases (38 eyes) of pigment dispersion syndrome in black individuals as defined by heavy deposition on the corneal endothelium and trabecular meshwork with increased intraocular pressure but no other ocular abnormalities. The 20 patients were a homogeneous group that was typified by older age distribution (average, 73 years), a preponderance of hyperopia (median refraction, +2.15 diopters spherical equivalent), female gender (19 women, one man), no iris transillumination defects (zero of 38 eyes), and flatter iris insertion into the ciliary body. We believe that this homogeneous group of black individuals with pigment dispersion and atypical features represents a pigment dispersion syndrome associated with older age, hyperopia, and female sex preponderance, in the black race.

THE PIGMENT dispersion syndrome, which is associated with glaucoma, heavy pigmentation of the trabecular meshwork, and Krukenberg spindles, was first described by Sugar and Barbour.[1] Later, radial midperipheral iris pigment epithelial defects were seen in patients with this syndrome.[2] These findings are associated with a secondary open-angle glaucoma that is found most commonly in young, myopic, white males.[3-7]

The pigment dispersion syndrome is thought to be rare in Orientals and almost nonexistent in blacks.[8,9] Five well-described cases in black patients have been published[2,10,11]; one of these patients had Waardenberg syndrome with blue irises, and the remaining four were young and had all of the classic manifestations of pigment dispersion syndrome, including Krukenberg spindles, heavy pigmentation of the trabecular meshwork, and myopia.

It was our clinical impression that pigment dispersion is not rare in the black population. To confirm this impression, we undertook a prospective survey in our glaucoma clinics for black patients with evidence of pigment dispersion syndrome, defined in terms of pigmented corneal endothelium and heavily pigmented trabecular meshwork. We found four patients who had clinical signs of classic pigment dispersion syndrome and identified an additional 20 patients who had clinical characteristics of what we believe is a newly described entity.

Patients and Methods

The population surveyed included black patients from the glaucoma services at the LSU Eye Center, Charity Hospital in New Orleans, Eye, Ear, Nose and Throat Hospital, and Ochsner Clinic, over a 12-month period, from December 1986 to December 1987. Patients with pigment deposition on the corneal endothelium of greater than 50 flecks of pigment and heavily pigmented trabecular meshwork were considered to have pigmentary dispersion syndrome. Patients with a history of uveitis, trauma, previous ocular surgery, previous anterior segment laser treatment, or any evidence of exfoliation material were excluded. Exfoliation material was sought with the slit lamp under high magnification predilation and postdilation, and evidence of both granular and pregranular forms of exfoliation or pupillary ruff atrophy was sought.

The initial examination included obtaining medical, ocular, and family histories, measuring visual acuity and manifest refraction, slit-lamp examination, gonioscopy, applanation tonometry, visual field examination, dilated

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slit-lamp examination, and dilated ophthalmoscopic examination. Slit-lamp photographs, gonioscopic photographs, and stereoscopic disk photographs were taken when possible. Iris transillumination was tested by fiberoptic scleral transillumination after dark adaptation in an unlighted room. The trabecular meshwork was graded on a scale ranging from 0 to 4+: 0 indicated no pigment; 1+, minimal to no pigment visible; 2+, moderate pigmentation; 3+, heavy pigmentation; and 4+, a dense black pigment band in the trabecular meshwork. In patients with a patchy distribution of pigment, the listed grade was defined as the maximum pigmentation covering at least 90 degrees of trabecular meshwork. Patients with at least 90 degrees of the trabecular meshwork graded 3+ were considered to have heavily pigmented meshwork. The presence or absence of diabetes was recorded. Patients were classified as having suspected glaucoma if they had increased intraocular pressure only or glaucoma if they had characteristic visual field defects or glaucomatous optic nerve cupping or both. All patients included in the survey were examined and graded by one examiner (S.F.B.) in a standard fashion.

Results

Twenty-four patients (46 eyes) of 1,217 patients examined were found to have heavy pigment deposition in the anterior segment and no history of uveitis, trauma, ocular surgery, anterior segment laser treatment, or evidence of exfoliation syndrome. History and chart review disclosed that three of the patients were diabetic. Fifteen patients were being followed up for glaucoma, three were followed up for ocular hypertension, and the remaining six were referred for examination. The findings for these 24 patients, including patient age, sex, diagnosis, iris transillumination, and degree of trabecular meshwork pigmentation, are given in Tables 1 and 2. The typical gonioscopic findings in patients with pigment dispersion syndrome are shown in the Figure.

Discussion

The 24 patients with the clinical features of heavy corneal endothelial pigmentation, usual-

TABLE 1
DATA ON PATIENTS WITH HYPEROPIC AGE-RELATED PIGMENTARY DISPERSION SYNDROME*

PATIENT NO., SEX, AGE (YRS)	REFRACTIVE ERROR (D) R.E.	L.E.	GLAUCOMA	TRABECULAR PIGMENTATION†
1, F, 81	+1.75	+1.00	Present	3+
				3+
2, F, 57	+2.50	+2.50	Absent	2+
				3+
3, F, 69	+3.75	+3.75	Absent	3+
				3+
4, F, 71	+2.00	+2.00	Present	2+
				3+
5, F, 76	+1.25	+0.75	Present	3+
				3+
6, F, 79	+7.25	+7.25	Present	3+
				3+
7, F, 73	+2.75	+2.75	Present	3+
				3+
8, F, 79	−0.75	−0.75	Present	3+
				3+
9, F, 71	+0.25	+0.25	Present	3+
				3+
10, F, 74	+1.75	+1.50	Present R.E.,	3+
			absent L.E.	3+
11, F, 80	NA‡	NA‡	Present	3+
12, F, 80	+4.00§	—	Absent	3+
13, F, 74	+4.25	+3.75	Present	3+
				3+
14, F, 67	+1.75	+2.00	Present	3+
				3+
15, F, 74	+2.50	+2.50	Present	3+
16, F, 59	+1.25	+1.25	Present	4+
				4+
17, F, 74	+2.00	+2.25	Present	4+
				4+
18, F, 69	+2.25	+2.00	Absent	3+
				3+
19, F, 81	+2.00‖	—	Present	3+
				3+
20, M, 79	+0.75	Plano	Present	4+
				4+

*No patients had transillumination defects, and all patients had Krukenberg spindles.

†1+ indicates minimal to no pigment visible; 2+, moderate pigmentation; 3+, heavy pigmentation; 4+, a dense black pigment band in the trabecular meshwork. First entry indicates right eye, second entry indicates left eye.

‡Not available.

§L.E. neovascular glaucoma (no light perception).

‖L.E. excluded because of previous surgery.

TABLE 2
DATA ON PATIENTS WITH CLASSIC PIGMENT DISPERSION*

PATIENT NO., SEX, AGE (YRS)	REFRACTIVE ERROR (D) R.E.	L.E.	GLAUCOMA	IRIS TRANSILLUMINATION DEFECTS
1, M, 23	−11.00	−12.75	Present	Absent
2, M, 47	−5.50	−5.50	Present	Absent
3, F, 21	−3.50	−2.75	Present	Present
4, F, 33	−1.00	−0.75	Absent	Absent

*All patients had Krukenberg spindles and a dense black pigment band covering at least 90 degrees of the trabecular meshwork.

ly in a Krukenberg pattern and heavy trabecular pigmentation, can be classified into two groups. The first group consisted of 20 patients with atypical characteristics: older age (57 to 80 years; average, 73 years), female predominance (19 women, one man), and hyperopic refraction (−0.75 to +7.25 diopters; average, +2.15 diopters, spherical equivalent). The remaining four patients had characteristics typical of the classic pigment dispersion syndrome: younger age (21 to 47 years; average, 31 years) and myopic refraction (−0.75 to −12.00 diopters; average, −5.31 diopters, spherical equivalent).

The first group of 20 patients differed significantly from patients with the classically described pigment dispersion syndrome.[8] In the first, atypical group, the trabecular pigment was generally graded at least 3+ in intensity, but was sometimes patchy in distribution. Pigmentation in the trabecular meshwork increases in density in response to many known conditions that were intentionally excluded in the study, including a history of uveitis, trauma, previous ocular surgery or anterior segment laser treatment, and any evidence of the exfoliation syndrome. Trabecular pigmentation also increases with advancing age, but is not ordinarily dense in the general population and is not significantly greater in black than white glaucoma patients.[12]

The atypical older patients failed to exhibit the peripheral concave bowing of the iris seen in the classic pigmentary dispersion syndrome[13]; in these older patients, although the angle was open to 10 to 25 degrees, the iris insertion was slightly below the scleral spur and was always flat or slightly convex.

Figure (Semple and Ball). Goniophotograph of Patient 6 shows a dense (3+) pigmentation of the trabecular meshwork. Note the pigmented Schwalbe's line.

Only one patient, a fair-complexioned man in the classic group, had iris transillumination defects. None of the 20 patients in the atypical group exhibited any transillumination defects. Although radial, midperipheral, slitlike iris transillumination defects are a major diagnostic feature in cases of pigment dispersion syndrome, these defects seem to be uncommon in black patients. In a series of 97 eyes with pigment dispersion syndrome reported by Scheie and Fleischhaver,[2] four eyes were of black patients. Only 12 of the 97 eyes did not exhibit transillumination defects; four of these 12 eyes were those of the black patients. Of the other three reported cases of black individuals with pigment dispersion syndrome, two studies failed to mention transillumination defects[2,10] and the third documented transillumination defects.[11]

Both lack of iris transillumination and older patients have also been described in other studies of pigmentary dispersion syndrome.[6,10] Scheie and Cameron[6] noted variable iris transillumination related to iris color: 25% of blue eyes and 68% of brown eyes lacked this phenomenon. Their study population also con-

tained many older patients, with a median age of 44 years in men and 54 years in women.[6]

Women with pigment dispersion syndrome generally constitute an older population than men with the syndrome.[14] Additionally, transillumination defects can disappear with time, and some of the patients in our series may represent pigmentary glaucoma in which defects have filled in with pigment after the active dispersion has stopped.[11]

It could be argued that our atypical group may comprise patients with primary glaucoma and secondary, unrelated pigment changes in the anterior segment. Barkan[15] found that pigment on the posterior surface of the cornea is more common (65% of eyes) in patients with glaucoma than in nonglaucomatous individuals, although the corneal pigmentation was rarely in the form of Krukenberg spindles as was typically found in our patients. It has also been suggested that Krukenberg spindles in elderly patients are an accentuation of an atrophic process unrelated to the primary glaucoma.[16] However, when Krukenberg spindles are an incidental finding in otherwise normal eyes, 88% of these eyes are myopic, and only 12% are hyperopic,[17] which is the opposite of the distribution in our patients.

The role of pigment in the pathogenesis of glaucoma is not completely clear. Some observers suggest that all pigmentary glaucoma is simply a variant of chronic open-angle glaucoma and that the pigment is not causally related.[18] Clinical and experimental evidence, however, suggests otherwise. Experimentally, pigment perfused into enucleated human eyes increased the resistance to aqueous outflow.[19] Clinically acute increases in intraocular pressure and decreases in outflow facility have been shown in patients with pigmentary dispersion who developed a shower of pigment.[20] Additionally, patients with pigmentary glaucoma followed up prospectively had a worsening of their glaucoma during active dispersion of pigment.[11] This evidence suggests that the pigment dispersion is at least one factor responsible for the glaucoma in our series of patients.

Because there are so many features that distinguish our atypical patients with pigmentary dispersion from those with the classic syndrome, we believe that this is a newly described entity of pigmentary dispersion syndrome in the black population. The source of the pigment dispersion in these individuals is not known. It may be related to their hyperopia with open angles. In classically described pigmentary dispersion syndrome, the packets of pigment are liberated from the posterior surface of the iris by mechanical rubbing of the zonular bundles on the peripherally posteriorly bowed iris.[19,21] In contrast, with a flat peripheral iris and a hyperopic lens, pigment release may be caused by the mechanical rubbing of the lens itself on the posterior surface of the iris. Transillumination might, therefore, appear to be less common because the iris pigment epithelial defect may be less complete with this form of trauma and because iris transillumination may be more difficult to observe in black individuals. Although we have not prospectively studied this, we suspect that pigment dispersion with hyperopia is not uncommon in older glaucoma populations of whites as well, and it may explain the heterogeneous findings in pigmentary dispersion syndrome reported in many large series.[2,6,11]

Twenty of the patients seemed to represent a homogeneous group of black patients with pigment dispersion and features with respect to age, gender, refractive error, and iris structure that are atypical of the classic syndrome. Nevertheless, the substantial pigment liberation in such eyes is a probable contributing factor in the development of glaucoma and should, therefore, be noted on physical examination. These patients are probably representative not only of other regional black populations, but perhaps of populations of whites and other races as well. We believe that this subset of patients with pigmentary dispersion syndrome has been previously unrecognized, partly because of the lack of iris transillumination defects; pigment dispersion without iris transillumination defects in an older population may represent a mechanism of pigment dispersion different from classically described pigmentary dispersion syndrome. How this pigment dispersion syndrome compares to simple chronic open-angle glaucoma and classic pigmentary dispersion syndrome in prognosis and response to therapy remains to be studied by prospective observation.

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OPHTHALMIC MINIATURE

Look for the two sets of whirligig eyes, one set higher than the other. In the water, one set lies above the surface film, the other below. This neat arrangement allows the whirligig to view prey and predator alike from above and below; it watches out primarily for preying fishes and birds, as do other surface film dwellers. Some view the eyes not as separate sets but as different parts of the same set. In this manner you might visualize whirligig eyes as natural bifocals.

Alan M. Cvancara, *At the Water's Edge*
New York, John Wiley & Sons, Inc., 1989, p. 88

Treatment of Foveal Pigment Epithelial Detachments With Contiguous Extrafoveal Choroidal Neovascular Membranes

Joseph I. Maguire, M.D., William E. Benson, M.D., and Gary C. Brown, M.D.

Fourteen eyes of 14 patients who had subfoveal retinal pigment epithelial detachments and extrafoveal contiguous choroidal neovascular membranes associated with age-related macular degeneration underwent laser photocoagulation treatment directed solely to their choroidal neovascular membrane. In eight of 14 eyes (57%), photocoagulation treatment resulted in closure of the choroidal neovascular membrane with subsequent collapse of the pigment epithelial detachment. Six of the eight eyes also had visual improvement. In six of 14 eyes (43%), the neovascular membrane eventually progressed into the fovea with resultant visual loss. The results of our study suggest that photocoagulation of extrafoveal choroidal neovascular membranes associated with foveal detachments of the retinal pigment epithelium may preserve and even improve visual function in affected patients.

THE MACULAR PHOTOCOAGULATION Study Group demonstrated the efficacy of argon laser photocoagulation treatment of choroidal neovascular membranes outside the foveal avascular zone in patients with age-related macular degeneration. The group excluded, however, all eyes with clinical or angiographic evidence of a retinal pigment epithelial detachment.[1,2] Although the Moorfields Macular Study Group noted retention of vision in three of six eyes with a choroidal neovascular membrane and an associated pigment epithelial detachment during 18 months of follow-up, larger series have failed to support this lack of progression.[3,4] Several retrospective series of both serous and nonserous pigment epithelial detachments have substantiated the poor visual prognosis in those eyes with choroidal neovascular membranes that were allowed to follow their natural course.[5-11]

Gass[12,13] was the first to identify the importance of choroidal neovascular membranes in causing pigment epithelial detachments (Fig. 1). He noted that treatment of a neovascular membrane in some cases could flatten a contiguous pigment epithelial detachment with preservation of vision.[12] Singerman[14] recently described 124 consecutive eyes with pigment epithelial detachments and associated neovascular membranes treated with laser photocoagulation. He divided the patients into four cate-

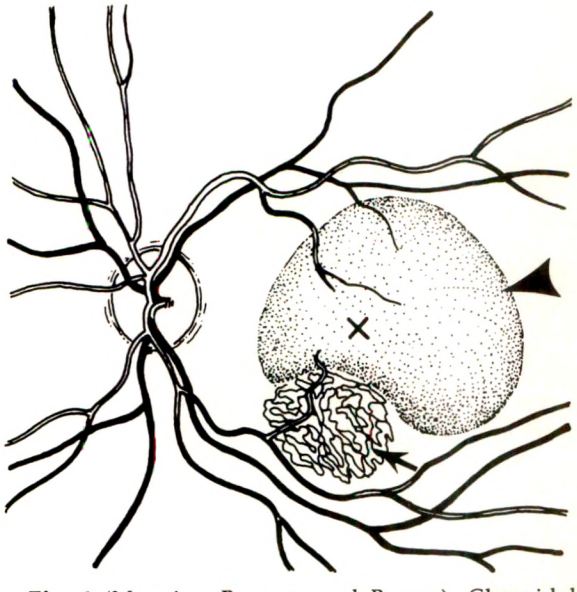

Fig. 1 (Maguire, Benson, and Brown). Choroidal neovascular membrane (arrow) with an adjacent subfoveal retinal pigment epithelial detachment (arrowhead).

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gories depending on the position of their pigment epithelial detachment or subretinal neovascular membrane or both. Although 48% of the eyes with subfoveal pigment epithelial detachments in his study had stable or improved visual function, the final visual acuity and individual degree of improvement were not specified.[14]

Patients and Methods

We studied 14 consecutive patients who had subfoveal pigment epithelial detachments and contiguous choroidal neovascular membranes and who were treated by two of us (W.E.B. and G.C.B.) in our institution between June 1982 and January 1988. All patients underwent a complete ocular examination, including history, visual acuity, slit-lamp and macular biomicroscopy, intravenous fluorescein angiography, and fundus photography. Data about pigment epithelial detachment size, fluorescein filling characteristics,[11] and distance of the neovascular membrane from the foveal avascular zone were recorded.

Inclusion criteria for the study included the following: a retinal pigment epithelial detachment involving the fovea; an angiographically defined contiguous choroidal neovascular membrane; a neovascular membrane greater than 200 μm from the foveal avascular zone center; patient age greater than 55 years; other clinical or fluorescein angiographic evidence of age-related macular degeneration; no evidence of alternate conditions associated with pigment epithelial detachments or choroidal neovascular membranes (such as ocular histoplasmosis, or angioid streaks)[13]; and visual acuity less than or equal to 20/40.

Argon green (514 nm) or krypton red (647 nm) wavelengths were used in treatment, and power settings were modified to give a gray-white to white burn. Treatment was performed only in eyes in which the choroidal neovascular membrane was contiguous with but did not extend beneath the pigment epithelial detachment on clinical and angiographic examination (Fig. 2). Eyes in which the choroidal neovascular membrane was thought to extend under the retinal pigment epithelial detachment (Fig. 3) were not included. Treatment was directed solely at the neovascular membrane.

Angiography was repeated at two- to three-week intervals after laser therapy, and additional treatment was applied until the neovascular membrane was successfully ablated. Laser photocoagulation was withheld and a lesion deemed untreatable if the neovascular process progressed into the foveal avascular zone. The follow-up visual acuity and time to retinal pigment epithelial detachment flattening were recorded (Table).

Treatment was considered successful if there was eradication of the subretinal neovascular membrane with flattening of the pigment epi-

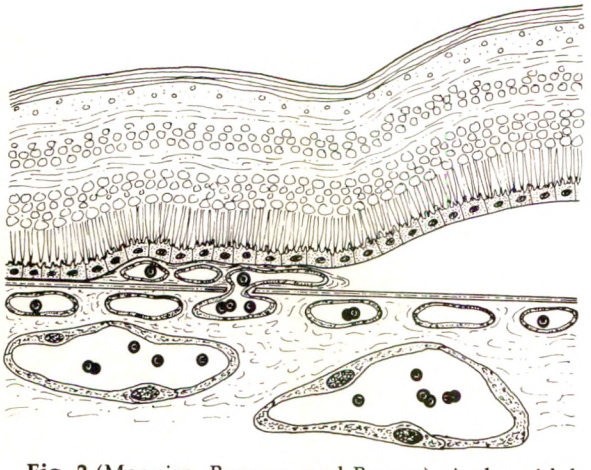

Fig. 2 (Maguire, Benson, and Brown). A choroidal neovascular membrane has broken through Bruch's membrane and is contiguous with an adjacent retinal pigment epithelial detachment. The neovascular focus has not extended within the pigment epithelial detachment.

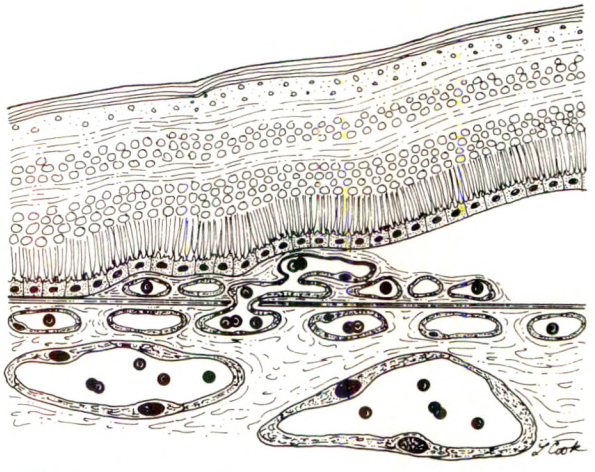

Fig. 3 (Maguire, Benson, and Brown). Extension of a choroidal neovascular membrane into the retinal pigment epithelial detachment. Interposed subpigment epithelial fluid interferes with precise localization of neovascular vessels.

TABLE

DATA ON PATIENTS WITH SUBFOVEAL RETINAL PIGMENT EPITHELIAL DETACHMENTS AND EXTRAFOVEAL CONTIGUOUS CHOROIDAL NEOVASCULAR MEMBRANES

PATIENT NO., AGE (YRS), SEX, EYE	VISUAL ACUITY*		TREATMENT RESULT	TIME TO RETINAL PIGMENT EPITHELIAL DETACHMENT FLATTENING (DAYS)	FOLLOW-UP TIME (MOS)
	INITIAL	FOLLOW-UP			
1, 63, F, L.E.	20/60	C.F.	Failure	—	—
2, 79, M, L.E.	20/60	C.F.	Failure	—	—
3, 79, M, L.E.	20/60	C.F.	Failure	—	—
4, †, F, L.E.	20/70	C.F.	Failure	—	—
5, 69, F, R.E.	20/30	20/80	Failure	—	—
6, 66, M, R.E.	20/70	20/70	Qualified success	12	6
7, 75, M, L.E.	20/200	20/200	Qualified success	14	6
8, 70, F, R.E.	20/50	20/25	Success	27	27
9, 76, F, L.E.	20/70	20/40	Success	62	7
10, 71, M, R.E.	20/50	20/25	Success	47	8
11, 68, F, R.E.	20/50	20/30	Success	47	57
12, 71, F, L.E.	20/60	20/20	Success	40	64
13, 75, M, R.E.	20/200	20/20	Success	6	15
14, 70, F, R.E.	20/50	C.F.	Failure	27	27

*C.F. indicates counting fingers.

†Age unknown.

thelial detachment and improvement of preoperative visual acuity. Patients were considered qualified successes if treatment succeeded in closure of their subretinal neovascular membrane with subsequent pigment epithelial detachment flattening, but resulted in no change of their visual acuity. Treatment was considered a failure if the retinal pigment epithelial detachment persisted or the neovascular membrane progressed within the foveal avascular zone despite treatment.

Results

Fourteen eyes of 14 patients had met our inclusion criteria and were treated with laser photocoagulation. The average patient age was 72 years (range, 63 to 79 years). Six eyes (43%) were considered successfully treated, six (43%) were failures, and two (14%) were qualified successes.

During this same treatment period, two of us (W.E.B. and G.C.B.) saw approximately 950 patients who had choroidal neovascularization caused by age-related macular degeneration. Our study group, therefore, comprised 1.6% of all cases of exudative age-related macular degeneration evaluated.

Patients who underwent successful treatment had a mean best-corrected preoperative visual acuity of 20/80 (range, 20/40 to 20/200). These eyes averaged 4.2 lines of improvement in Snellen visual acuity. The mean follow-up period was 29.7 months (range, seven to 64 months). Posttreatment time until pigment epithelial detachment flattening averaged 37 days (range, six to 62 days). One eye (Case 14) underwent successful laser photocoagulation treatment with visual acuity improvement that remained stable for two months. A new recurrence of subretinal neovascularization within the fovea, however, subsequently reduced visual acuity to less than 20/400, and this eye was ultimately classified as a treatment failure.

In the six eyes with treatment failures, choroidal neovascularization progressed within the foveal avascular zone despite laser photocoagulation. Cases 6 and 7 were classified as qualified successes because both underwent successful closure of their neovascular membrane and flattening of the associated pigment epithelial detachment, but without improvement or worsening of visual acuity.

Comparison of pigment epithelial detachment dimensions between treatment failures and successes disclosed an average diameter 18% greater in eyes with treatment failures (3.60 mm vs 2.95 mm). Likewise, the average

distance from the choroidal neovascular membrane to the foveal avascular zone center was 36% less in treatment failures (440 μm vs 690 μm).

All eyes had delayed fluorescein filling of their pigment epithelial detachments[11]; none developed a pigment epithelial tear at the time of treatment or during the follow-up period.

Discussion

Our study, although limited in number and retrospective in nature, illustrates the following: treatment of a choroidal neovascular membrane with a contiguous foveal pigment epithelial detachment can help improve and stabilize visual acuity; flattening of a foveal pigment epithelial detachment can be associated with improvement in visual acuity; and in at least some eyes, the source of subpigment epithelial fluid in a pigment epithelial detachment is an associated choroidal neovascular membrane.

Casswell, Kohen, and Bird[11] classified retinal pigment epithelial detachments into four groups on the basis of the fluorescein angiographic appearance in an attempt to identify morphologic features that have prognostic value.[11] Group I consists of pigment epithelial detachments with early hyperfluorescence, and group II are those with late hyperfluorescence. Group III pigment epithelial detachments are shallow with limited fluorescence (drusen type), and Group IV lesions have an irregular hyperfluorescence.

Eyes with large, foveal retinal pigment epithelial detachments are at high risk for developing severe visual loss[5]; there are several possible outcomes. A pigment epithelial detachment may undergo spontaneous flattening. Unfortunately, this is generally associated with a decrease in vision.[3,11] Most pigment epithelial detachments undergoing spontaneous flattening are of the early fluorescent variety. Second, a choroidal neovascular membrane and associated disciform process may occur, which is common in the late or irregular fluorescent group. Third, 10% of eyes may develop a pigment epithelial rip; such eyes are associated with slow filling defects.[11] Finally, a pigment epithelial detachment may remain unchanged indefinitely.[11] All eyes included in our study had pigment epithelial detachments with late or irregular filling characteristics.

Several strategies for treating pigment epithelial detachments have been reported.[3,8,9,15] Initial treatment protocols involved placing a row of burns along the temporal edge of the detachment.[15] Later, the Moorfields Macular Study Group performed a controlled trial of argon laser photocoagulation by using a grid or scatter treatment over the pigment epithelial detachment. Such treatment was not found to be beneficial and yielded worse visual results than observation alone.

Only persistent retinal pigment epithelial detachments in patients 55 years of age and older are consistently associated with good visual acuity.[11] Spontaneous or iatrogenic flattening of pigment epithelial detachments almost always results in loss of vision. In our study, however, successful treatment of a contiguous neovascular process often resulted in rapid reattachment of the pigment epithelium and improved visual acuity. Although it is difficult to rule out extension of a choroidal neovascular membrane under detached pigment epithelium, neovascular membranes that do not extend under the pigment epithelial detachment are easier and safer to treat, because laser energy is not dispersed by intervening subretinal pigment epithelial fluid (Fig. 3). Dispersal of laser energy by this fluid layer would make obliteration of an underlying neovascular membrane more difficult and would increase the risk of tearing of the elevated retinal pigment epithelium.

There is debate about the temporal association of pigment epithelial detachments and choroidal neovascular membranes. It has been proposed that the pigment epithelial detachment is the initial event followed by the secondary development of a neovascular membrane.[10,11,16] Others have suggested the presence of an occult choroidal neovascular membrane not seen clinically or with fluorescein angiography.[13] There is evidence that the pigment epithelium itself is the main contributor to the fluid within certain pigment epithelial detachments associated with older patients. Pfeffer, Usukura, and Bok[17] showed that monolayers of pigment epithelial cells form spontaneous domes of fluid when cultured on plastic. This fluid production by the retinal pigment epithelium, along with the decreased hydraulic conductivity through the lipid-laden Bruch's membrane of an eye with age-related macular degeneration, may result in a pigment epithelial detachment.[11,18] This would imply that spontaneous or postlaser treatment flattening of serous retinal pigment epithelial detachments is secondary to severe metabolic failure of the

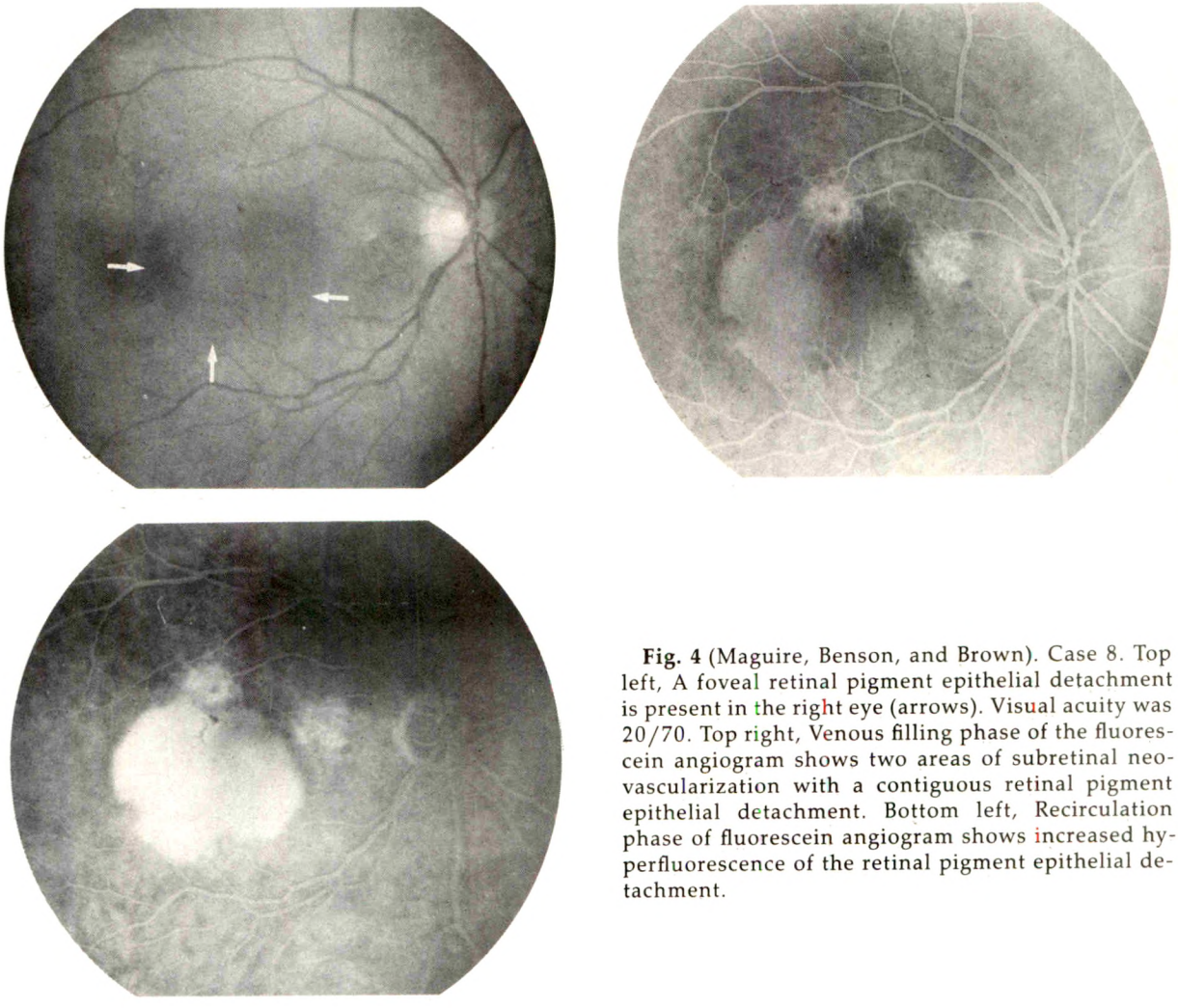

Fig. 4 (Maguire, Benson, and Brown). Case 8. Top left, A foveal retinal pigment epithelial detachment is present in the right eye (arrows). Visual acuity was 20/70. Top right, Venous filling phase of the fluorescein angiogram shows two areas of subretinal neovascularization with a contiguous retinal pigment epithelial detachment. Bottom left, Recirculation phase of fluorescein angiogram shows increased hyperfluorescence of the retinal pigment epithelial detachment.

pigment epithelium. Our study implies, however, that in some pigment epithelial detachments, the source of subpigment epithelial fluid is a contiguous neovascular membrane (Fig. 4) and resolves with successful closure of the subretinal neovascularization (Fig. 5). The pigment epithelium in these individuals would still be metabolically intact and capable of supporting the overlying photoreceptors when reapproximated, which would result in improvement, or at least stabilization, of visual function.

The Macular Photocoagulation Study showed that treatment of choroidal neovascular membranes outside of the foveal avascular zone in patients with age-related macular degeneration helps prevent or postpone visual morbidity. Their protocol, however, excluded eyes with associated pigment epithelial detachments. Our study demonstrates that the presence of an extrafoveolar subretinal neovascular membrane with a contiguous pigment epithelial detachment is not necessarily a contraindication to laser photocoagulation treatment. Indeed, when treatment was directed solely at the neovascular membrane in eight of 14 eyes (57%), not only was the neovascular membrane successfully obliterated, but the pigment epithelial detachment flattened with improvement or stabilization of visual acuity.

Singerman and Stockfish[19] found that 65% of their age-related macular degeneration patients with foveal pigment epithelial detachments and associated choroidal neovascular complexes had a visual acuity less than 20/200 at one-year follow-up. Poliner and associates[6] noted that 78% of their patients with choroidal neovascular membranes and associated pig-

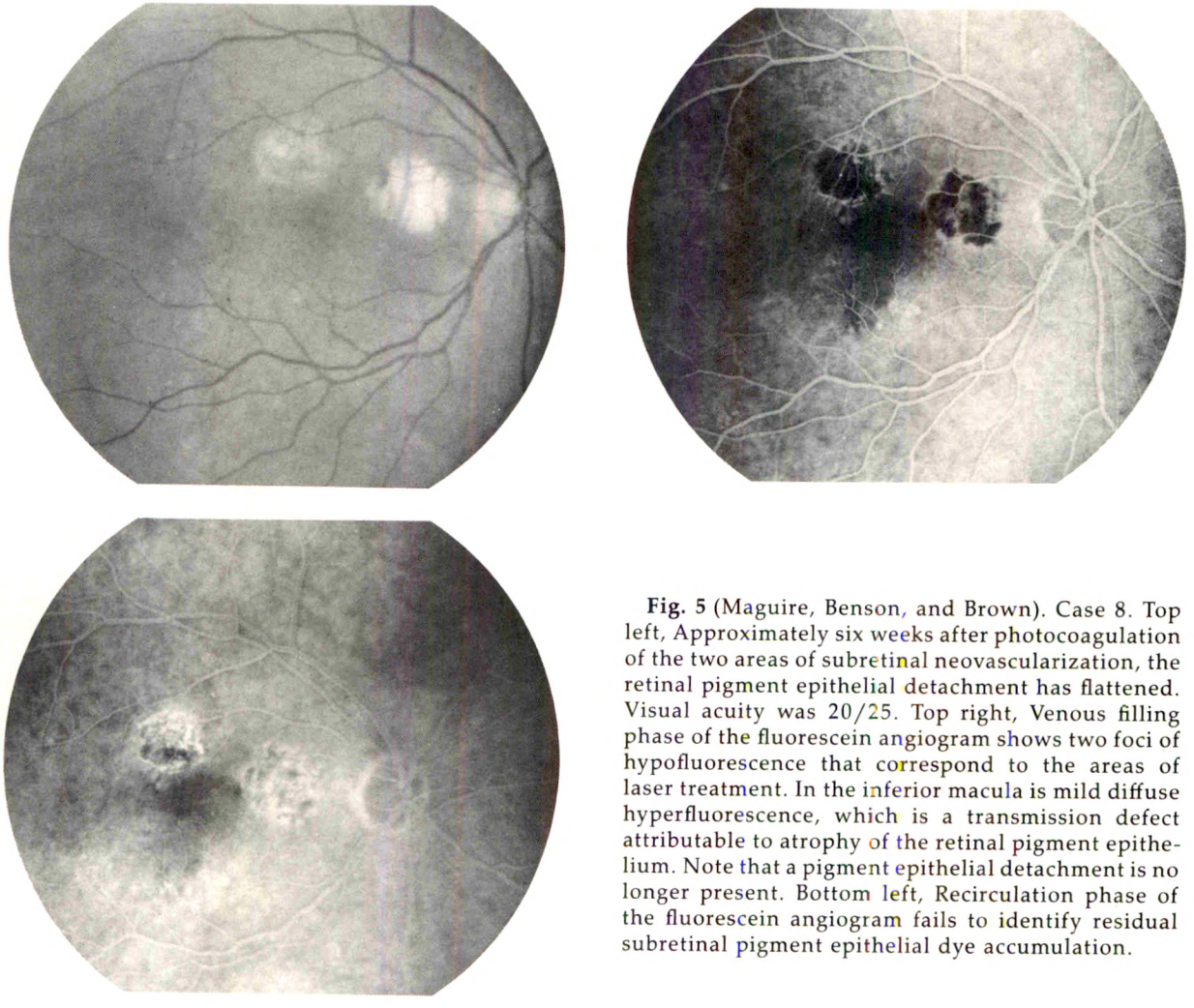

Fig. 5 (Maguire, Benson, and Brown). Case 8. Top left, Approximately six weeks after photocoagulation of the two areas of subretinal neovascularization, the retinal pigment epithelial detachment has flattened. Visual acuity was 20/25. Top right, Venous filling phase of the fluorescein angiogram shows two foci of hypofluorescence that correspond to the areas of laser treatment. In the inferior macula is mild diffuse hyperfluorescence, which is a transmission defect attributable to atrophy of the retinal pigment epithelium. Note that a pigment epithelial detachment is no longer present. Bottom left, Recirculation phase of the fluorescein angiogram fails to identify residual subretinal pigment epithelial dye accumulation.

ment epithelial detachments developed a visual acuity of 20/200 to counting fingers within a 12-month period. Only one eye in their series maintained a visual acuity of 20/50 or better. Additionally, Elman and associates[7] showed that 76% of eyes with macular pigment epithelial detachments and a visual acuity of 20/200 or less had evidence of a choroidal neovascular membrane. Meredith, Braley, and Aaberg[5] also reported that even without angiographically associated choroidal neovascularization, there is a poor visual prognosis for patients over 55 years of age with eyes with serous detachments of the pigment epithelium extending into the fovea. When compared to the natural course of juxtafoveal subretinal neovascular membranes without pigment epithelial detachment, and foveal pigment epithelial detachments alone in eyes with age-related macular degeneration, aggressive laser photocoagulation treatment seems a viable alternative for those eyes with a foveal pigment epithelial detachment and a contiguous extrafoveal subretinal neovascular membrane.

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Combined Exfoliation and Pigment Dispersion Syndrome

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Both exfoliation syndrome and pigmentary dispersion syndrome can lead to secondary glaucoma. We treated five patients who had pigmentary dispersion and who subsequently developed exfoliation. In one patient who had bilateral pigment dispersion syndrome, the presence of exfoliation increased the difficulty of controlling intraocular pressure in the affected eye. In a monocular patient, exfoliation and pigmentary dispersion were concurrently present with characteristic defects of both pigmentary dispersion and exfoliation as seen by transillumination defects of the iris. A third patient had bilateral pigmentary dispersion and uncontrollable intraocular pressure in an eye with exfoliation. Despite argon laser trabeculoplasty, the pressure remained uncontrolled. Another patient had a filtering operation in the left eye, with gradually increasing intraocular pressure in the right eye. Exfoliation material complicated the pressure control in the unoperated on eye. Another patient had an eight-year history of glaucoma in the left eye for which filtering surgery was performed. Exfoliation was present in both eyes with controlled pressure in the filtered eye but uncontrolled pressure in the nonfiltered eye.

EXFOLIATION (pseudoexfoliation) syndrome and pigment dispersion syndrome are discrete clinical entities that have a number of similarities, including pigment dispersion throughout the anterior segment, pigment liberation upon pupillary dilation, increased trabecular pigmentation, and iris transillumination defects.[1-3] When correlated with an age-corrected population, there is an increased incidence of open-angle glaucoma in both disorders.[4-6]

Pigment dispersion syndrome is most commonly seen in young to middle-aged adults and is associated with myopia.[7-9] Exfoliation found in older patients has no correlation with refractive error and is characterized by flecks of white material on the lens surface, zonular fibers, and ciliary body.[1,10]

Because these disorders are fairly common and occur in different age groups, it would not be unusual to find exfoliation syndrome developing in a patient who previously had pigment dispersion syndrome.

Case Reports

Case 1

A 49-year-old woman had exfoliation syndrome in the right eye. Despite therapy with timolol and pilocarpine, her intraocular pressure increased to 42 mm Hg in her right eye and remained between 16 and 18 mm Hg in the left eye. On a subsequent visit, she was found to have midperipheral, slitlike, radial transillumination defects in both irides. The presence of exfoliation syndrome increased the difficulty of controlling intraocular pressure in this patient with bilateral pigment dispersion syndrome.

Case 2

A 55-year-old man had increased intraocular pressure in the right eye. The left eye was phthisical after a long-standing retinal detachment. A Krukenberg spindle was present on the cornea of the right eye. Two types of iris transillumination defects were noted: midperipheral, radial, slitlike defects characteristic of pigment dispersion syndrome, and diffuse, patchy de-

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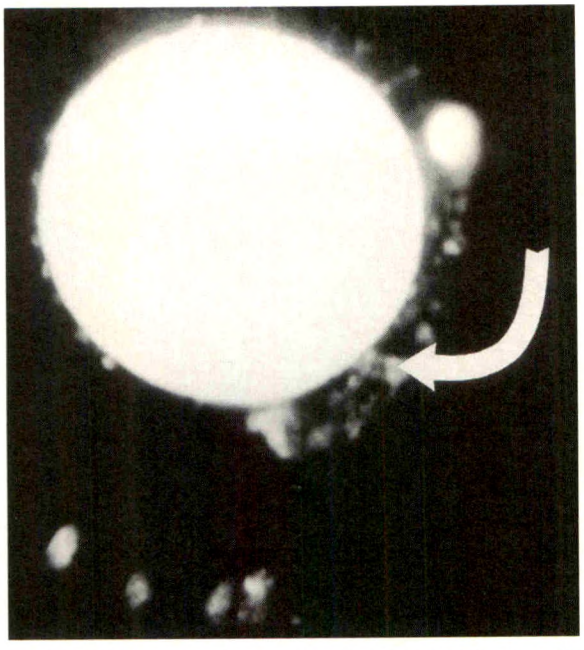

Fig. 1 (Layden and associates). Case 2. Iris transillumination pattern shows midperipheral, slitlike, radial defects characteristic of pigment dispersion syndrome and patchy iris sphincter transillumination characteristic of exfoliation syndrome (arrow).

fects at the sphincter region and pupillary border with loss of the pupillary ruff (Fig. 1). A ring of exfoliation material was visible on the anterior lens capsule of the right eye after dilation (Fig. 2). The patient's intraocular pressure was 28 mm Hg. The angle was widely open, and focal deposits of exfoliation material could be seen on the heavily pigmented trabecular meshwork (Fig. 3).

Case 3

In a 58-year-old man, pigmentary glaucoma was diagnosed in both eyes with bilateral midperipheral, slitlike, radial iris transillumination defects and Krukenberg spindles. He was placed on a regimen of topical and systemic medications of increasing dosages, and when these did not control intraocular pressure successfully, he underwent argon laser trabeculoplasty over 360 degrees of the trabecular meshwork in the right eye and 180 degrees in the left eye. Despite maximal medical therapy, intraocular pressure was R.E.: 30 mm Hg and L.E.: 18 mm Hg. Exfoliation material was subsequently noted on the lens capsule of the right eye. The exfoliation adversely affected intraocular pressure control.

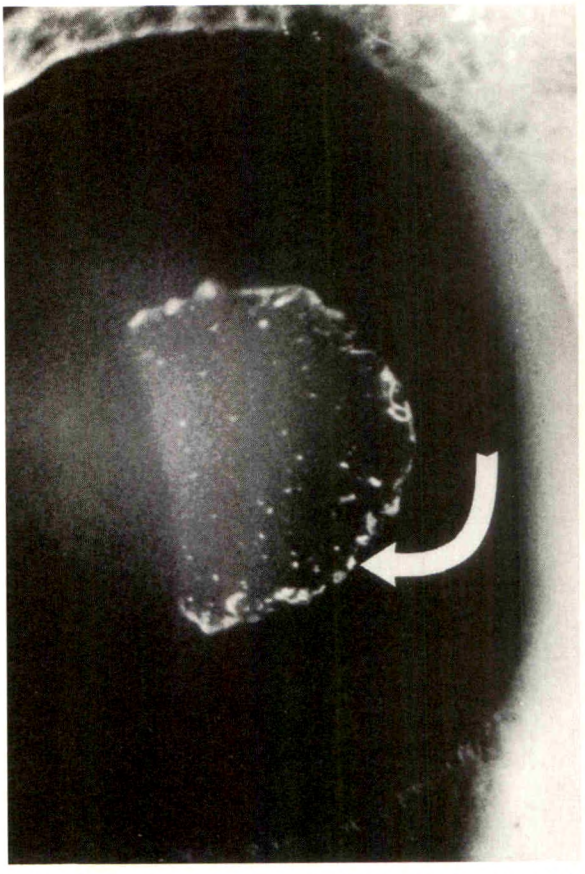

Fig. 2 (Layden and associates). Case 2. Central disk of exfoliation material with prominently curled edges visible after pupillary dilation (arrow).

Case 4

A 57-year-old man with a nine-year history of glaucoma had undergone trabeculectomy in the left eye and had gradually increasing intraocular pressure in the right eye. His brother also had glaucoma, and his daughter had pigment dispersion syndrome. On examination, the patient had bilateral Krukenberg spindles and midperipheral, slitlike, radial iris transillumination defects. Intraocular pressure was R.E.: 26 mm Hg and L.E.: 14 mm Hg. The angles were widely open, and there was dense pigmentation of the trabecular meshwork in the right eye and mild pigmentation in the left. Exfoliation material was noted on the lens surface in the right eye.

Case 5

A 64-year-old man had an eight-year history of glaucoma in the left eye, for which trabeculectomy had been performed. One year previ-

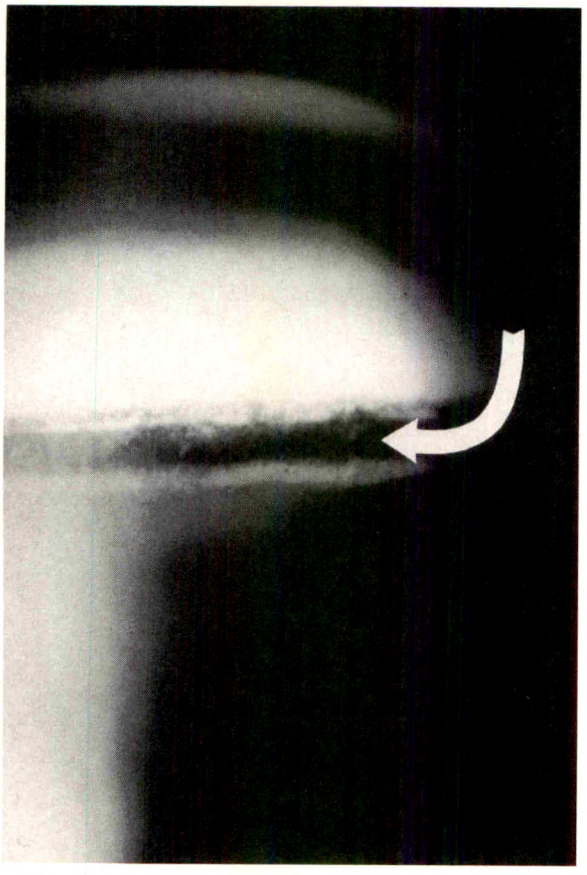

Fig. 3 (Layden and associates). Case 2. Flakes of exfoliation material are present on the densely pigmented trabecular meshwork (arrow).

ously, intraocular pressure in the right eye had begun to rise. Slit-lamp examination disclosed Krukenberg spindles and midperipheral, slitlike, radial iris transillumination defects bilaterally and, in the left eye, patchy transillumination defects of the iris sphincter region. Intraocular pressure was R.E.: 30 mm Hg and L.E.: 15 mm Hg. Gonioscopy disclosed wide open angles with dense pigmentation over the trabecular meshwork and a pigment ring on the posterior lens surface at the site of zonular insertion in both eyes. Exfoliation material was visible on the ciliary processes and zonules of both eyes (Fig. 4). The cup/disk ratio was 0.3 in the right eye and 0.9 in the left.

Discussion

Pigment dispersion syndrome and exfoliation syndrome are distinct clinical entities that have

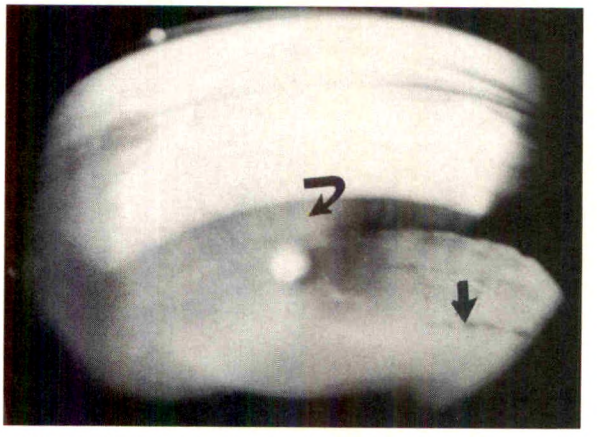

Fig. 4 (Layden and associates) Case 5. Increased pigmentation of the trabecular meshwork occurs in both pigment dispersion and exfoliation syndromes. Exfoliation material is present on the zonules (curved arrow), and a pigment ring on the posterior lens surface at the site of zonular insertion is characteristic of pigment dispersion syndrome but not exfoliation syndrome (straight arrow).

several features in common, most notably the liberation of pigment from the iris pigment epithelium and its deposition on structures throughout the anterior segment. Pigment dispersion syndrome typically occurs bilaterally, whereas exfoliation more commonly occurs unilaterally.

The detection of pigment dispersion is usually between 25 and 50 years of age, whereas exfoliation is typically found in patients over 60 years of age. The male/female predominance in pigmentary dispersion is two to one, and the incidence is equal in exfoliation. Usually pigmentary dispersions involve eyes bilaterally, whereas exfoliation is unilateral in over 50% of patients. The pigmentation on the corneal endothelium is well known as a Krukenberg spindle in pigment dispersion, whereas corneal pigment dispersion with exfoliation is patchy and follows no particular pattern. Iris transillumination defects in pigmentary dispersion are radial and slitlike and usually occur in the midperiphery, whereas in exfoliation there is usually a loss of sphincter pigment epithelium with patchy transillumination of the pupillary margin. The trabecular meshwork in pigmentary dispersion has a characteristic, dense, uniform pigment; in exfoliation, although there is increased pigmentation in the meshwork, it is splotchy and irregular. In pigment dispersions, the refractions are usually on the myopic side, whereas there is no trend for refractive errors in

exfoliation patients. Pigment dispersion usually occurs in white patients unlike exfoliation, which affects all races equally. In pigmentary dispersion, the angles are wide and deep with a deep recess and folding of the iris over the concavity of the lens equator. In exfoliation patients, although most of the angles seen are open, there may be a number of eyes with narrow or occludable angles.

In pigment dispersion syndrome, the posterior pigment epithelium of the iris rubs against the zonular bundles, liberating pigment, the deposition of which in the trabecular meshwork leads to increased intraocular pressure.[11] Exfoliation syndrome appears to be secondary to an age-related degenerative process that affects components of the basement membrane.[12] In exfoliation syndrome, both exfoliation material and liberated iris pigment are deposited in the trabecular meshwork.

Both exfoliation and pigment dispersion can occur without associated glaucoma. Increased intraocular pressure associated with either of these entities, however, is usually more severe and difficult to treat and has a worse patient prognosis than it does in primary open-angle glaucoma.[13-17]

Exfoliation syndrome is common, and its prevalence increases with age, occurring in several percent of the population over age 70 years.[18-20] One would expect the syndrome to develop in patients who had previously developed pigment dispersion syndrome, with or without glaucoma.

Because many cases of pigment dispersion syndrome, particularly those in which glaucoma does not develop, go undetected, often the diagnosis is made incidentally after the patient has been found to have increased intraocular pressure in one eye secondary to the development of exfoliation. In other patients, pigmentary glaucoma may develop in the patient's 30s or 40s, but intraocular pressures normalize and glaucomatous damage stabilizes after pigment liberation ceases.[21,22] Such a situation may be misinterpreted as a recrudescence of the original glaucoma or, if the initial episode had never been diagnosed, it may be interpreted as exfoliation in one eye and low-tension glaucoma in the other eye. Still, other patients may have pigmentary glaucoma that requires medications for control of intraocular pressure, and the glaucoma may be regarded as uncontrolled when exfoliation develops in one eye but is not noted.

In some patients, the exfoliation may be prominent, but the diagnosis of pigment dispersion may be uncertain. With age, the signs of pigment dispersion syndrome (Krukenberg spindles, iris transillumination defects, and dense pigmentation of the trabecular meshwork) tend to regress. Because this disorder appears to be hereditary,[23] examination of family members may help to verify the diagnosis.

Our patients had increased difficulty of control of glaucoma in eyes with pigment dispersion and exfoliation. The combination of these two forms of glaucoma represents a difficult management problem because of fluctuating intraocular pressure and resistance to therapy. Judging the stability of the intraocular pressure accurately is especially important.

One should suspect the coexistence of exfoliation and pigment dispersion syndromes when there is asymmetric pigmentation between the two eyes or if the control of intraocular pressure is more difficult in one eye than the other. When a patient has bilateral pigment dispersion but asymmetric intraocular pressures, one should consider an underlying cause that may commonly occur unilaterally, such as exfoliation. The clinician should be aware of the possible coexistence of exfoliation and pigment dispersion syndromes to aid in the proper diagnosis and ultimate therapy of these two difficult types of glaucoma.

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OPHTHALMIC MINIATURE

A woman of an incredible old age—brown, wizened features, sunken eyes, black kimono, carved wooden cane—gazed at him with expressionless eyes from the steps of a temple as he ran his hand slowly over sand in the courtyard, over the stone lantern near a bent tree, the intricate carving on a pillar; watched him until he turned and caught her eye and inclined his head to her in a barely perceptible nod, and she closed and opened her eyes in acknowledgment of some shared secret message that had passed between them.

Chaim Potok, *The Book of Lights*
New York, Fawcett Crest, 1982, p. 329

Visual Function Improvement in Patients With Macroprolactinomas Treated With Bromocriptine

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We studied eight patients who had visual field defects secondary to prolactin-secreting macroadenomas and who had improved visual function with bromocriptine treatment without surgery or radiation. We recommend bromocriptine as a primary treatment for prolactin-secreting macroadenomas. If therapy is effective, continued regular neuro-ophthalmologic, endocrine, and imaging studies are necessary, because treatment with bromocriptine must be continued indefinitely.

In the 1970s, surgical resection, with or without supplemental radiation, was the preferred treatment for pituitary adenomas. For the last decade, however, bromocriptine, which is a dopamine agonist that can reduce the size of certain pituitary tumors, has been used extensively to treat prolactin-secreting microadenomas without surgery.[1] The role of bromocriptine in the long-term treatment of macroprolactinomas, however, is still uncertain. Some believe that bromocriptine should be used as a preliminary treatment before surgery, whereas others use bromocriptine as the sole treatment for macroprolactinomas.

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Material and Methods

We studied eight patients who had prolactin-secreting macroadenomas. Each patient underwent neuro-ophthalmic examination, including Goldmann visual fields or automated perimetry or both. Endocrine evaluation of each patient included prolactin and growth hormone levels and thyroid function tests. All patients underwent either computed tomography or magnetic resonance imaging studies of the pituitary region. All patients were examined before treatment.

Dosage regimens of bromocriptine ranged from 5.0 to 25.0 mg/day. Patients were examined at intervals of three to 12 months with repeated visual field measurements, imaging studies, and prolactin measurements.

Case Reports

Case 1

In September 1986, a 41-year-old man noted blurred vision in the left upper quadrant in his left eye. His visual acuity was 20/20 in both eyes, and the results of his ophthalmic examination were reportedly normal. In December 1986, the patient noted decreased vision in his left eye. On reexamination, his visual acuity was R.E.: 20/20 and L.E.: counting fingers at 5 feet; he had a left relative afferent pupillary defect with normal motility, slit-lamp examination results, and ocular tensions. Visual fields showed a temporal defect in the right eye; both disks were flat and pink. The patient had long-term decreased libido and diminished beard growth. Computed tomography showed a pituitary mass with suprasellar extension; his prolactin level was 3,820 ng/ml. He was treated

with 7.5 mg of bromocriptine three times daily without side effects. Within three days, the patient's visual acuity in his left eye improved to 20/20, and his prolactin level decreased to 49 ng/ml. Visual fields improved to within normal limits by February 1987. His visual acuity, visual fields, and prolactin level have remained normal since then. Follow-up imaging studies have shown a significant reduction in the size of the suprasellar mass.

Case 2

A 59-year-old left-handed man initially consulted an endocrinologist in 1986 for evaluation of lethargy. His physician found a prolactin level of 2,100 ng/ml; computed tomography disclosed a pituitary adenoma with extension into the suprasellar area and the cavernous sinus on both sides, with destruction of the clivus. His ocular history included amblyopia in the left eye and myopic astigmatism in both eyes.

The patient's visual acuity was R.E.: 20/25 + 1 and L.E.: 20/40 − 1. Both pupils were of equal size and reactive without afferent pupillary defect. Goldmann visual fields showed bitemporal defect to the I-2 and I-3. His disks were flat and pink. The patient was started on a regimen of 2.5 mg of bromocriptine, with a final dosage of 7.5 mg/day, with no side effects. His prolactin level decreased to 10 ng/ml within two months. With treatment, his visual acuity improved and has remained at R.E.: 20/15 and L.E.: 20/25 with normal visual fields.

Case 3

A 68-year-old man noted progressive painless loss of vision in his right eye over many years concomitant with decreased libido and decreased beard growth. Examination in April 1985 disclosed a visual acuity of R.E.: counting fingers at 10 feet and L.E.: 20/25. There was a right afferent pupillary defect. Visual fields showed a bitemporal defect, which was greater on the right than on the left; both disks were flat and pink without pallor. The patient's prolactin level was 5,264 ng/ml; a computed tomographic scan showed a large sellar mass with suprasellar extension (Fig. 1, left). After treatment with bromocriptine, 5 mg/day, his prolactin level fell to 410 ng/ml, and his visual acuity improved to R.E.: 20/25 within three days. By October 1986, the mass decreased in size significantly; suprasellar extension was no longer present. Since then, his visual acuity, visual fields, and prolactin level have remained normal. Follow-up imaging studies showed marked regression of the tumor (Fig. 1, right).

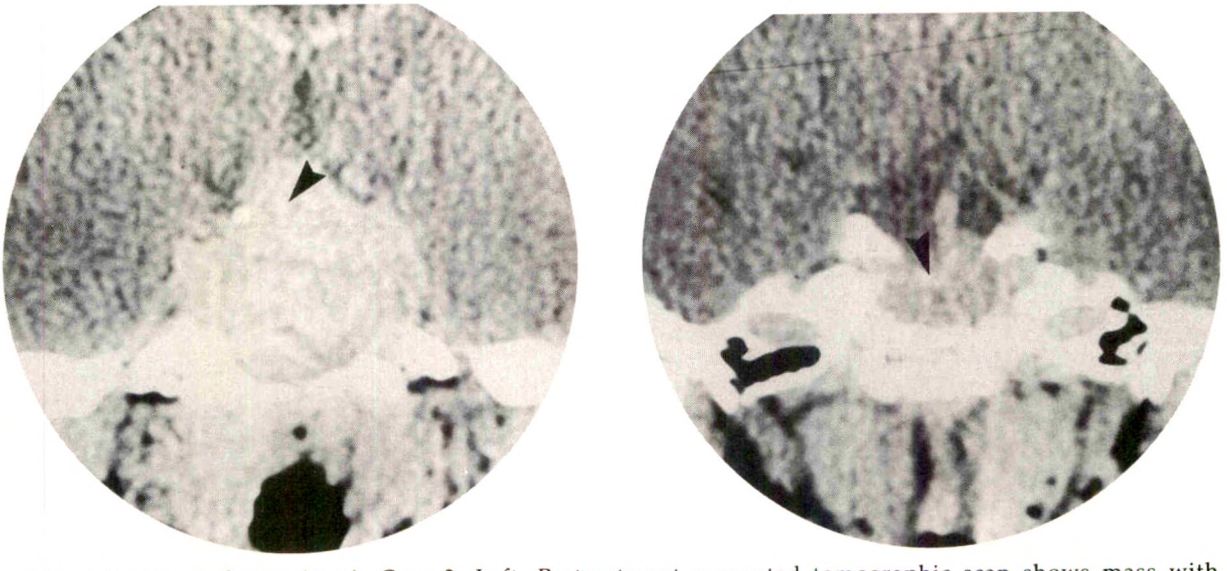

Fig. 1 (Lesser and associates). Case 3. Left, Pretreatment computed tomographic scan shows mass with suprasellar extension (arrow). Right, Posttreatment computed tomographic scan shows reduction in size of mass (arrow).

Case 4

A 61-year-old man with a 23-year history of glaucoma complained of decreased vision of one month's duration in the right eye. In August 1987, his visual acuity was R.E.: 20/100 − 1 and L.E.: 20/25. A right afferent pupillary defect was present. Visual fields showed diffuse depression in the right eye and a superotemporal defect in the left eye. The patient missed all Hardy-Rand-Rittler color plates on the right and 2½/6 on the left. Ocular tensions were 28 mm Hg in both eyes. Both eyes had disk pallor, which was greater on the right than on the left, with glaucomatous cupping. A computed tomographic scan showed a large pituitary adenoma with extension into the suprasellar cistern, middle cranial fossa, and nasal cavity posteriorly; involvement was greater on the right than on the left. The patient's prolactin level was 41,000 ng/ml. After treatment with 7.5 mg/day of bromocriptine, his prolactin level decreased to 1,160 ng/ml by October 1987 and 37 ng/ml by September 1988. Follow-up visual acuity was R.E.: 20/30 and L.E.: 20/15. His visual fields improved with a remaining inferior arcuate defect in his right eye and a less dense temporal defect in his left eye. Follow-up computed tomography showed further reduction in the size of the mass. His course has remained unchanged.

Case 5

A 57-year-old man had been aware of blurred vision temporally, initially in the right eye and later in the left eye, for three to four years associated with peripheral visual field loss (Fig. 2). In early 1985, he became aware of intermittent episodes of diplopia, particularly at near, with occasional loss of letters while reading. He also noted decreases in libido and beard growth.

In June 1985, the patient's visual acuity was R.E.: 20/30 and L.E.: 20/25; his pupils were equal in size and reactive to light with no afferent pupillary defect. Dyschromatopsia was demonstrated in both eyes by using Hardy-Rand-Rittler plates; both disks were pale. Eye movements and saccades were within normal limits; the eyes were orthophoric. Diplopia was secondary to the visual field defects. The patient's prolactin level was 348 ng/ml. A large intrasellar mass, with suprasellar extension and homogenous enhancement, which is consistent with a pituitary adenoma, was seen on computed tomography (Fig. 3).

After treatment with 7.5 mg/day of bromo-

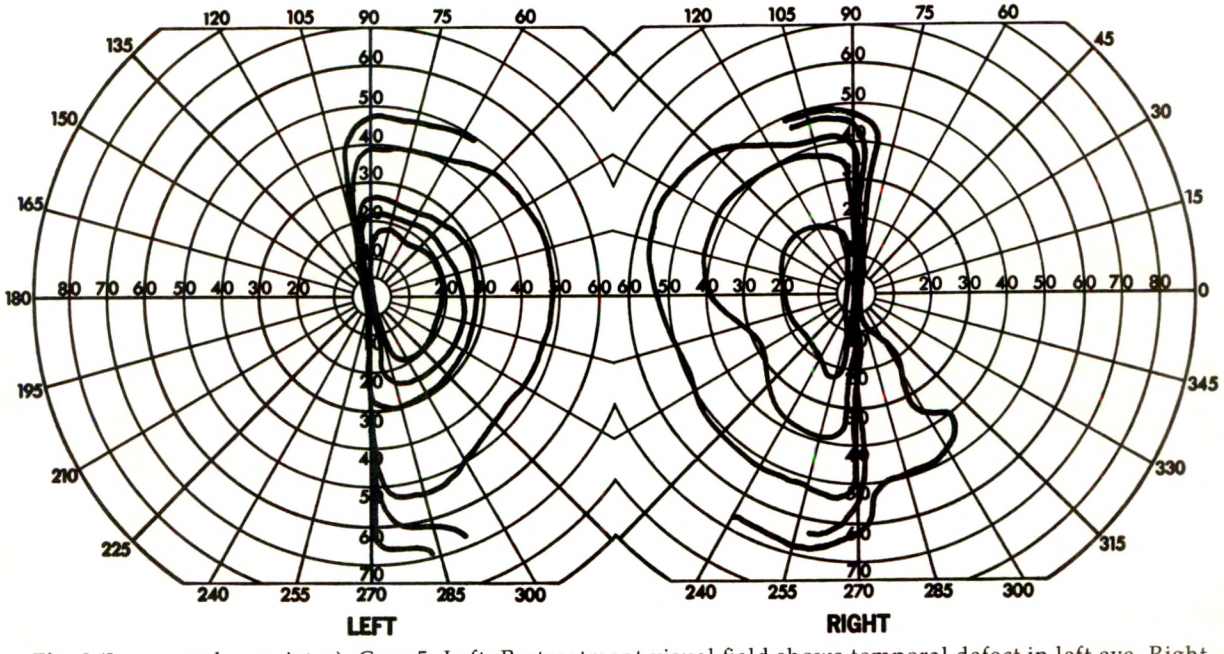

Fig. 2 (Lesser and associates). Case 5. Left, Pretreatment visual field shows temporal defect in left eye. Right, Pretreatment visual field shows temporal defect in right eye.

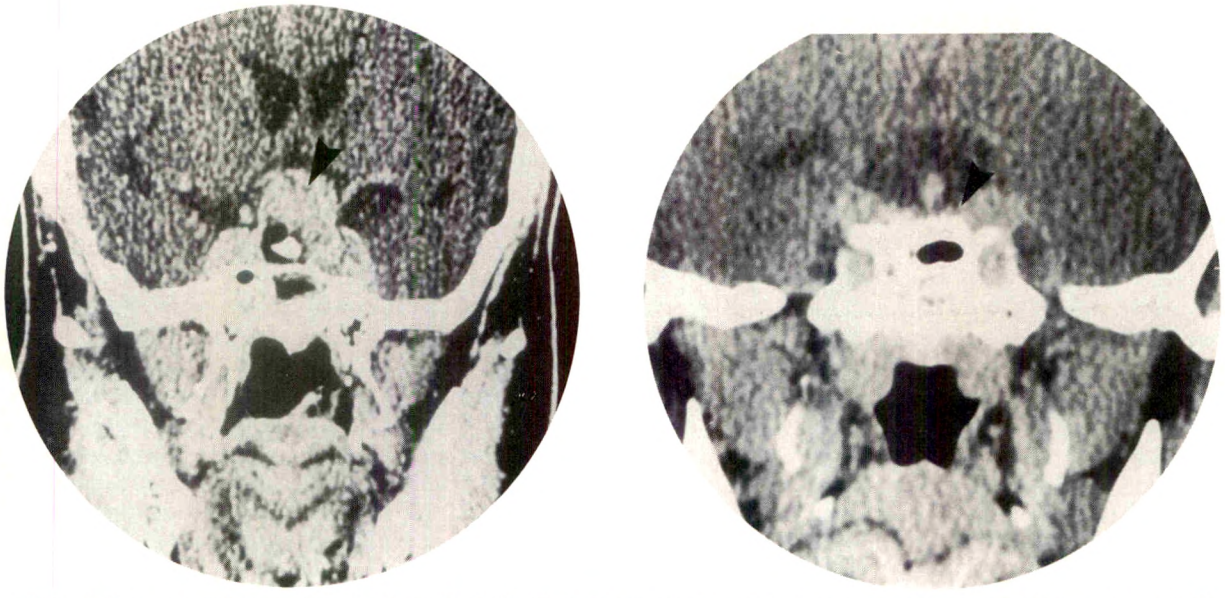

Fig. 3 (Lesser and associates). Case 5. Left, Pretreatment computed tomographic scan shows mass with suprasellar extension (arrow). Right, Posttreatment computed tomographic scan shows reduction in size of mass (arrow).

criptine, the patient's prolactin level decreased to 6 ng/ml. His visual field defects improved dramatically after five days with retention of bitemporal defects only to small test objects (Fig. 4). Visual acuity improved to R.E.: 20/20 and L.E.: 20/25. A follow-up computed tomographic scan in December 1985 showed marked reduction in the suprasellar extension with an intrasellar mass still present (Fig. 3, right). The patient has remained on medication with no side effects and with normal prolactin levels. His visual function has remained stable.

Case 6

In March 1986, a 26-year-old woman with a two-year history of amenorrhea, associated with dull throbbing frontal headaches, was examined. Visual acuity was 20/20 in both eyes. She had a left paracentral scotoma, but the results of her ocular examination were otherwise normal. Her prolactin level was 3,800 ng/ml; computed tomography disclosed a pituitary mass with suprasellar extension. She was treated with bromocriptine, up to 25 mg/day, with a decrease in her prolactin level to 340 ng/ml. She had fewer headaches and less fatigue. A posttreatment computed tomographic scan in December 1984 showed a decrease in size of the pituitary adenoma with normal vision and visual fields. Because the patient did not wish to take medication three times daily indefinitely, she elected to undergo transsphenoidal hypophysectomy. Surgery was uncomplicated; no increased bleeding or fibrosis were noted. No side effects from the medication had been reported before surgery.

Case 7

A 55-year-old man had decreased vision in the left eye and decreased libido, impotence, and a right supraorbital headache. When examined in September 1985, his visual acuity was R.E.: 20/20 and L.E.: 20/40. He had a left afferent pupillary defect and dyschromatopsia in both eyes. He had a left inferior incongruous homonymous hemianopsia; motility and disks were normal. A skull x-ray showed increased size of the sella turcica; a computed tomographic scan showed an intrasellar lesion with extension to the right cavernous sinus, suprasellar and over the right optic tract. His prolactin level was 2,249 ng/ml.

On Oct. 15, 1985, the patient was started on 2.5 mg/day of bromocriptine, which was increased to 2.5 mg three times a day over four days. Three days later, his prolactin level fell to

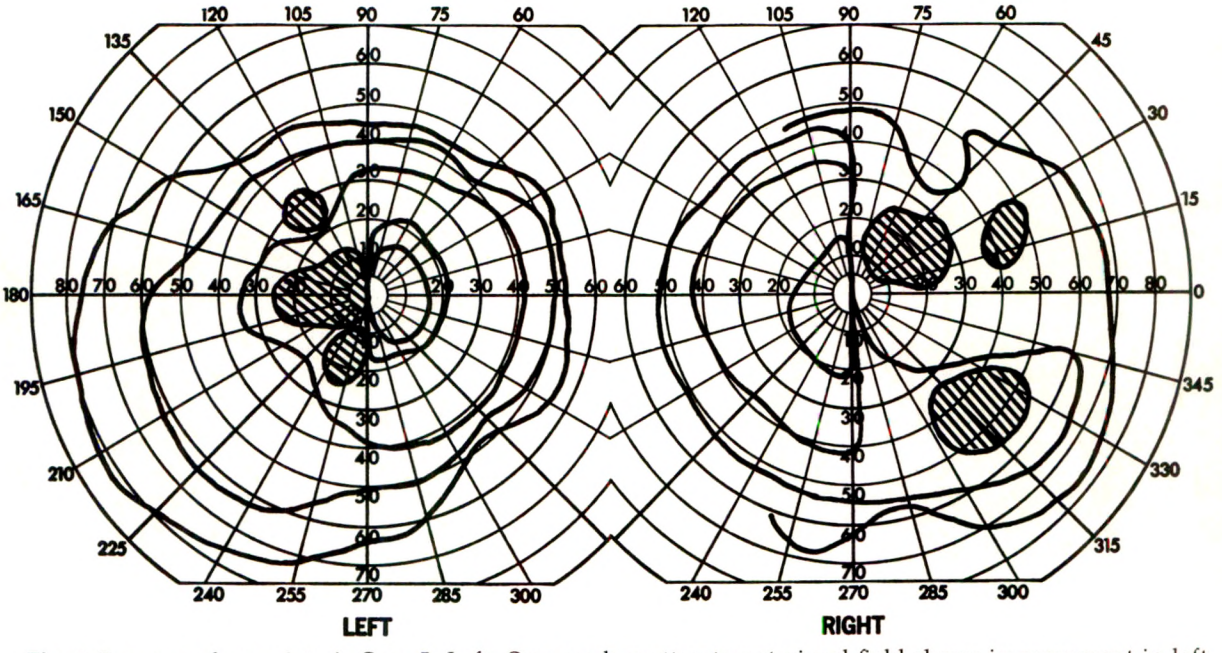

Fig. 4 (Lesser and associates). Case 5. Left, One-week posttreatment visual field shows improvement in left eye. Right, One-week posttreatment visual field shows improvement in right eye.

181 ng/ml, his visual acuity improved to 20/20 in both eyes, visual fields improved, and headaches were absent. A computed tomographic scan done in February 1986 showed a 60% decrease in tumor size. The patient's prolactin level decreased to 30 ng/ml. The patient had no side effects from bromocriptine. His visual acuity and visual fields have remained normal. Follow-up imaging studies showed a small amount of tissue within the sella turcica only. The patient's prolactin level in September 1989 was 4 ng/ml.

Case 8

A 59-year-old man noted painless progressive visual loss in his left eye which had begun in March 1988. In May 1988, his visual acuity was R.E.: 20/25 − 1 and L.E.: 20/60 − 2; he missed two Hardy-Rand-Rittler plates on the right and four plates on the left. Pupils were equal in size and reactive, and there was a trace left afferent pupillary defect. The right disk was flat and pink; the left disk showed temporal pallor. He had an asymmetric bitemporal field defect, which was much worse on the left than on the right. His prolactin level was 5,500 ng/ml. Computed tomography showed a pituitary adenoma with superior and inferior extension. The patient was treated with 2.5 mg of bromocriptine three times daily. Visual acuity returned to 20/20 in both eyes within three months. His visual field initially showed a decrease in temporal depression; three months after the onset of treatment, the visual fields were within normal limits. A magnetic resonance imaging scan six months later showed that the mass was still present in the sella turcica but with minimal suprasellar extension. A scan one year later showed that there was no suprasellar extension, but there was still some extension to the left sphenoid sinus. The patient's prolactin level one month after the initiation of treatment was 200 ng/ml and was 85 ng/ml 12 months later.

Results

The ages of the patients ranged from 26 to 59 years; seven of the patients were men. Patients were followed up from one to four years after the initial treatment. Pretreatment prolactin levels ranged from 348 ng/ml to 41,000 ng/ml.

Endocrine symptoms included decreased libido, decreased beard growth, absent hair growth, and lethargy in men and amenorrhea with galactorrhea in the woman. Five patients had blurred vision, five had bitemporal defects, one had a homonymous quadrantanopsia, and one had a paracentral scotoma. Dosage of bromocriptine ranged from 5 mg/day to 25 mg/day. In most patients, improvement in visual fields and visual acuity occurred within a few days of treatment. One patient's treatment was complicated by headache, fatigue, and light-headedness. There were no reports of cerebrospinal fluid rhinorrhea. In two patients whose visual acuity was counting fingers before treatment, visual acuity improved to 20/25 in one patient and 20/20 in the other patient within one week. Follow-up imaging studies showed significant reduction in the size of the tumor. Prolactin levels decreased dramatically in all patients. The female patient eventually had surgery because of her reluctance to take bromocriptine on a long-term basis.

Discussion

In the early part of the century, pituitary adenomas were classified by staining pattern, which was either basophilic, acidophilic, or chromophobic.[2,3] Since the early 1970s, however, with the development of immunocytochemical staining techniques, pituitary tumors are now classified by hormonal production (for example, prolactin-secreting adenomas, growth hormone–secreting adenomas, or corticotropin-secreting adenomas.[4]

Prolactinomas are the most common type of pituitary adenoma, accounting for 40% to 50% of all pituitary adenomas in most studies. Affected women often have amenorrhea and galactorrhea. In men, the symptoms are more subtle and usually consist of decreased libido, decreased beard growth, fatigue, and, occasionally, awareness of field defects.[5,6] Microadenomas are tumors confined within the sella turcica; macroadenomas are tumors that have extended beyond the sella turcica. In men, most prolactinomas are macroadenomas, which are often associated with both visual acuity loss and visual field defects. Most microadenomas respond to bromocriptine; 90% of patients recover reproductive function associated with lowering of the prolactin level.[7,8]

Six of the eight patients had blurred vision with bitemporal visual field defects, one had a homonymous quadrantanopsia, and one had a paracentral scotoma. Follow-up ranged from 18 to 56 months. Medication has remained effective in all patients.

In our patients with prolactin-secreting macroadenomas, return of visual function was rapid, with improvement of both vision and visual fields often occurring within a few days (Figs. 2 and 4). Prolactin levels decreased rapidly in most patients. Only one patient had side effects from the bromocriptine, which included fatigue and light-headedness. One patient chose surgery because of her desire not to take medication indefinitely.

Bromocriptine is an ergot derivative that binds to dopamine receptors with five to ten times greater affinity than dopamine.[9] The effective dose ranges from 5 to 25 mg/day. A study on over 1,000 pregnancies indicates that it is not teratogenic.[10] Bromocriptine causes tumor shrinkage in 60% to 75% of macroprolactinomas with size reduction averaging 50% to 70%.[11,12] Bromocriptine decreases both the nuclear and cytoplasmic size, but it is not cytotoxic.[13] In most patients, the drug is tolerated well when it is instituted gradually. When first started, there is often temporary nausea and orthostatic dizziness. Other side effects include headache, fatigue, abdominal cramps, cerebrospinal fluid rhinorrhea, nasal congestion, and constipation. Adverse effects can be minimized by starting with a low dose, usually 1.25 mg/day taken at bedtime. The dose may then be increased until the desired therapeutic response occurs, with the most common regimen being 2.5 mg three times daily.[14] Disadvantages of the drug include its expense (over $1.00 per pill) and the need for long-term usage of three pills per day, because the drug is tumoristatic rather than tumoricidal.[15] Dopamine is an endogenous, hypothalamic inhibitor of prolactin secretion in the pituitary gland. Increases of prolactin level may be associated with the empty sella syndrome, or other processes that interfere with dopamine action or transport. Lesions in or near the hypothalamus, such as tumors, infiltrative disease, or sarcoidosis, and radiation are associated with increased prolactin levels. Drugs that decrease dopamine production, such as neuroleptics, antihypertensives, and the antidepressant, amoxapine, may increase serum prolactin level. Usually, however, prolactin levels above 200 ng/ml are only asso-

ciated with pregnancy or a prolactinoma. Other causes of increased prolactin levels include hypothyroidism, cirrhosis, chronic renal failure, chest wall lesions, and breast stimulation.[16]

In 1975, Corenblum and associates[17] demonstrated the antitumor effect of bromocriptine in two patients who had pituitary tumor. Vaidya and associates[18] described three patients who had pituitary tumors and who had improvement of visual fields after treatment with bromocriptine.[18]

Landolt, Wuthrich, and Fellmann[19] described improvement in a patient on bromocriptine who had third and fourth nerve paresis associated with recurrent pituitary adenoma. There have been numerous subsequent reports that document clinical and radiographic evidence of tumor regression with the use of bromocriptine.[20-31] Grimson and Bowman[21] and other investigators documented dramatic tumor regression and suggested that bromocriptine be used before surgery.[22-26] Woodhouse, Khouqueer, and Sieck[27] reported improvement of visual field defects after treatment with bromocriptine. Other investigators, however, have suggested that long-term treatment with bromocriptine might cause fibrosis of the pituitary tumor, which would lead to more difficult surgical excision.[28] Barrow and Tindall[6] suggested that treatment with bromocriptine softened the tumors and made them easy to remove with suction. Warfield and associates[30] reported improvement in levels of thyroid hormone, growth hormone, and cortisol levels, and speculated that improvement may be secondary to decompression of the pituitary tumor. At least three cases of tumor recurrence while patients were being treated with bromocriptine have been reported.[32] Some investigators have reported pituitary apoplexy with long-term bromocriptine treatment.

In a multicenter study reported by Molitch and associates,[31] treatment with bromocriptine for prolactin-secreting macroadenomas was evaluated in 27 patients. The investigators found that tumor size was reduced by more than 50% in 12 of the patients and to about half of original size in five patients. In the remaining ten patients, the extent of tumor reduction was less; there were no patients in whom the tumors grew during therapy. Although decreases in prolactin levels usually preceded decrease in size of the tumor, there was no correlation between size reduction and decrease in prolactin level. Prolactin levels returned to normal in 12 of the 16 women and in six of the 11 men. As in other series, there was usually a rapid decrease in tumor size; 19 of the patients had marked reductions within six weeks. In eight patients, however, significant reduction occurred only after six months. Molitch and associates[31] recommended that treatment be tried for at least six months before it is considered a failure. In their series, nine of the ten patients with visual field defects had improvement. They recommended that surgery be reserved for patients who do not respond to medical treatment.

Moster and associates[33] described ten patients who had prolactin-secreting tumors and who were treated with bromocriptine. Nine of these patients had improved visual fields or visual acuity, with evidence of decrease in tumor size and reduction of serum prolactin level. In most patients, visual improvement usually occurred within a few days of starting bromocriptine. All patients in their series were men. One patient had cerebrospinal fluid rhinorrhea that occurred 15 months after treatment and that required repair of a dural defect and transsphenoidal hypophysectomy. One patient also had transsphenoidal hypophysectomy with visual field worsening after surgery. There are a few studies that measure the long-term effectiveness of transsphenoidal hypophysectomy in macroprolactinomas. Serri and associates[34] studied 16 patients who had macroprolactinomas and who were treated with transsphenoidal hypophysectomy. They found that relapse of hyperprolactinemia was frequent and often delayed by several years. The prolactin levels of 11 of the 16 patients indicated that they were not cured surgically. Of the five patients who had normal prolactin levels after surgery, four had relapse of hyperprolactinemia within three years. In neither group, however, was there radiologic evidence of tumor recurrence. Even though prolactin levels were increased, they were low enough for pregnancy to occur. Other series have shown normal postoperative prolactin levels in 45% to 70% of patients.[5] Many patients with macroadenomas require postoperative radiation therapy, which increases the risk of the onset of hypopituitarism within two years after treatment.[35]

Although about 73% of patients with macroprolactinomas have reduction in tumor size with the use of bromocriptine,[11] no patient in our series did not respond to bromocriptine. We recommend that patients with macroprolactin-

omas start treatment with 2.5 mg of bromocriptine per day and that the dose be increased to up to 15 to 20 mg/day over a two- to three-week period. If there is no improvement in visual function or no reduction in tumor size within three months, transsphenoidal hypophysectomy may be indicated. Treatment with bromocriptine must be continued indefinitely because the medication is not cytotoxic, and the tumor will recur with discontinuation of the medication. If medical therapy is effective, continued regular neuro-ophthalmologic, endocrine, and imaging studies are necessary.

Our study, as well as other studies,[32,34] indicates that the response of macroprolactinomas to bromocriptine treatment is rapid, effective, and associated with few side effects. We recommend bromocriptine as the primary treatment for patients who have macroprolactinomas and impaired visual function.

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OPHTHALMIC MINIATURE

She had not seen Ezra clearly since the spring of '75, four and a half years ago, when she first started losing her vision. She'd had a little trouble with blurring. She went to the doctor for glasses. It was arteries, he told her; something to do with her arteries. She was eighty-one years old, after all. But he was certain it could be treated. He sent her to a specialist, who sent her to someone else . . . well, to make a long story short, they found they couldn't help her. Something had shriveled away behind her eyes. "I'm falling into disrepair," she told the children. "I've outlived myself." She gave a little laugh.

Anne Tyler, *Dinner at the Homesick Restaurant*
New York, Berkley Books, 1983, pp. 2 and 3

Unusual Mucopolysaccharide Disorder With Corneal and Scleral Involvement

Chloe T. C.-Winterbotham, M.D., Elise Torczynski, M.D., Allen L. Horwitz, M.D., Beatrice Y. J. T. Yue, Ph.D., and Ramon L. Font, M.D.

A 68-year-old man and a 66-year-old woman had diffuse corneal stromal deposits that stained with alcian blue and colloidal iron but did not react with periodic acid-Schiff stain and lipid stains. Similar deposits were found within postmortem sclera in one case, but not in other ocular or extraocular tissues. The abnormal material was sensitive to testicular hyaluronidase and chondroitinase. The material reacted with monoclonal antibody 9-A-2 after digestion by chondroitinase AC in one case and ABC in both cases, which is consistent with the identification of the glycosaminoglycans chondroitin 4-sulfate and dermatan sulfate. Electron microscopic examination of the cornea in both cases disclosed granular material in vacuoles dispersed extracellularly and, rarely, in keratocytes. Results of blood and skin fibroblast enzyme assays for clinically relevant mucopolysaccharidoses and mucolipidoses were normal in both patients, and there were no somatic abnormalities suggesting a storage disease.

CORNEAL STROMAL OPACITIES caused by excess accumulation of glycosaminoglycans occur in a number of ocular and systemic diseases such as macular corneal dystrophy,[1-17] systemic mucopolysaccharidoses,[4,9-13,16-20] systemic mucolipidoses,[9-12] fleck corneal dystrophy,[4,9,11] and in corneal wound healing and scarring.[4,5,21]

Glycosaminoglycans (also known as acid mucopolysaccharides) can be identified histochemically by positive staining with cationic dyes,[4,7-9,11] by determining sensitivity to degradative enzymes such as hyaluronidases and chondroitinases,[4,22-25] and by staining with monoclonal antibodies against either the unsaturated disaccharides formed by enzyme digestion or the sulfated epitopes.[6-8,22,26-28]

We studied scleral and stromal corneal opacities that stained with colloidal iron but did not react with periodic acid-Schiff stain. Methods used to characterize the abnormal material indicated that the deposits had characteristics of the glycosaminoglycans, chondroitin sulfate, and dermatan sulfate. The histopathologic and biochemical features of our cases differed from those described either in localized corneal dystrophies or in systemic diseases with similar corneal findings.

Case Reports

Case 1

A 68-year-old man had had a peripheral ring of corneal haze since infancy. He had dry eyes but good vision until after age 60 years.

At age 68 years, best-corrected visual acuity was R.E.: 20/80 and L.E.: 20/80. On examination, fine ground-glass opacities with intervening haze were found throughout the corneal stroma extending from corneoscleral limbus to corneoscleral limbus, with the periphery more opaque than the central cornea bilaterally (Fig. 1). There was lagophthalmos with ectropion, and several corneal dry areas stained bilaterally. In the temporal right cornea, there was neovascularization. Moderate nuclear sclerosis

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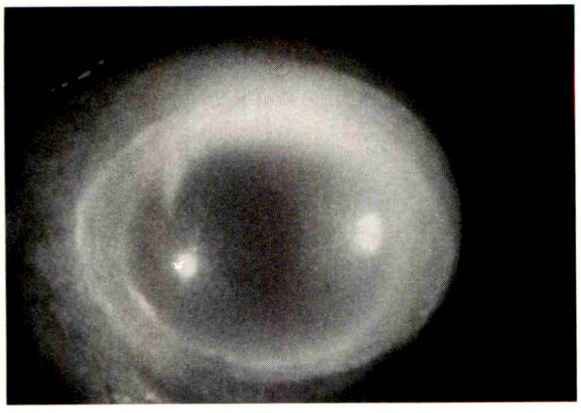

Fig. 1 (Winterbotham and associates). Case 1. Slit-lamp photograph of left cornea. Stromal opacities are more concentrated peripherally than centrally.

and cortical cataracts were present bilaterally. The ocular fundi were normal.

The patient underwent penetrating keratoplasty and cataract extraction in the right eye. Postoperatively, vision remained poor, and the patient died a year later. The eyes and limited extraocular tissues were obtained after death for study.

The patient's physical characteristics and mental status were normal. Osteoarthritis and cardiovascular disease began after age 50 years. A myocardial infarction at age 56 years resulted in congestive heart failure with secondary renal failure and vascular hypertension. When the patient was in his 30s, he was treated for syphilis. The patient reported that a deceased paternal aunt in Central America had had a corneal ring opacity similar to his since childhood (Fig. 2); there was no known consanguinity.

Case 2

A 66-year-old woman had photophobia and punctate keratitis noted since age 11 years with corneal opacities extending across the palpebral fissures bilaterally. The results of the remainder of the ocular examination were normal in each eye. At age 49 years, the patient had bilateral superficial keratectomies after her visual acuity had decreased to 20/200 in both eyes. Visual acuity improved to 20/70 in both eyes postoperatively. Penetrating keratoplasty was performed in the left eye at age 57 years, when visual acuity was L.E.: 20/70, and in the right eye at age 63 years, when visual acuity was R.E.: 20/200. Postoperatively, visual acuity improved to R.E.: 20/40 and L.E.: 20/30.

The patient's physical characteristics and mental status were normal. Osteoarthritis and atherosclerosis developed after age 60 years. Significant previous illnesses included tuberculosis treated at age 30 years and malaria. There was no family history of corneal haze and no known consanguinity.

Material and Methods

The corneal buttons from the penetrating keratoplasties from the right eyes of both patients were placed in 10% formalin and processed for light microscopy. Representative specimens were placed in 1% glutaraldehyde and processed for electron microscopy. At autopsy in Case 1, the right globe was placed in 10% formalin and the left globe in ethanol, and both globes were processed for light microscopy. Sections of the heart, aorta, lungs, liver, kidney, and spleen were stained with hematoxylin and eosin and periodic acid-Schiff stain.

Sections of the corneas in both cases were stained with hematoxylin and eosin, periodic acid-Schiff stain, Masson trichrome, Congo red, mucicarmine, Prussian blue, toluidine blue, alcian blue at pH 0.4 and 2.5, and colloi-

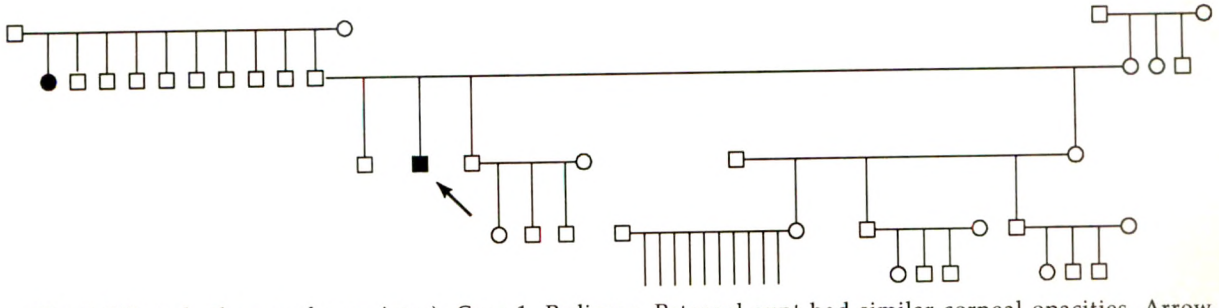

Fig. 2 (Winterbotham and associates). Case 1. Pedigree. Paternal aunt had similar corneal opacities. Arrow shows proband.

dal iron. Cryostat sections of the formalin-fixed cornea from Case 1 were tested with Sudan black, oil red O, and Schultz's cholesterol method.

Based on positive staining with alcian blue and colloidal iron, sections and controls were tested with enzymes that digest glycosaminoglycans, including *Streptomyces* hyaluronidase (Sigma Chemical Co., St. Louis, Missouri), testicular hyaluronidase,[24] and chondroitinase ABC and AC.[25] Testing with chondroitinase ABC and AC was repeated to compare the sections from Case 1 to positive controls (normal human dermis and cartilage frozen sections). Deparaffinized cornea and sections of the right globe from Case 1 and positive controls were treated at 37 C either with 0.2 U/ml chondroitinase ABC or AC (Seikagaku Fine Biochemicals, Seikagaku Kogyo, Ltd., Tokyo, Japan) in 0.1 M enriched Tris-HCl buffer, pH 8.0, or with buffer alone (negative control) for four hours.[25] Sections were rinsed with normal saline and stained with colloidal iron.

Immunohistochemical staining was performed on the cornea and right globe in Case 1 and the cornea from Case 2. A whole eye and two corneas from individuals aged 60 years, 22 months, and 72 years of age, respectively, were the normal controls. The control tissues were fixed in 10% formalin, embedded in paraffin, and processed in the same manner as the patient's tissues. Monoclonal antibody 9-A-2, which recognizes 4-sulfated chondroitin sulfate and dermatan sulfate,[26,27] was used (ICN Immunobiologicals, Lisle, Illinois). The antibody is raised against chondroitinase ABC-digested rat chondrosarcoma proteoglycans and reacts with the resulting unsaturated disaccharide near the linkage region between the oligosaccharide and the core protein.[26,27] The specificity of the antibody recognition relies on the previous digestion of antigens on tissue sections with either chondroitinase ABC or AC.[26] For the staining, all the deparaffinized sections were treated at 37 C with either 0.2 U/ml chondroitinase ABC or buffer alone (negative control) for two hours, as described. Sections were rinsed with phosphate-buffered saline and incubated for ten minutes on ice in a 10% normal goat blocking serum. They were subsequently allowed to react for 45 minutes with monoclonal antibody 9-A-2 (1:10 dilution). After a 20-minute rinse with phosphate-buffered saline, tissue sections were incubated for 45 minutes with biotinylated goat anti-mouse IgG (1:500, Vector Laboratories, Burlingame, California), rinsed with phosphate-buffered saline, placed in 0.3% H_2O_2-methanol for 30 minutes to inactivate intrinsic peroxidase, incubated for 60 minutes in avidin-biotin horseradish peroxidase complex (Vector Laboratories), and developed in 0.01% H_2O_2, 0.05%, 3, 3'-diaminobenzidine tetrahydrochloride (Sigma Chemical Co.) in 0.05 M Tris-HCl buffer, pH 7.4, as previously described.[28] The sections were counterstained with hematoxylin, mounted in glycerin jelly, and photographed. Based on positive results, the same procedure was repeated in Case 1 after digestion with chondroitinase AC by using the remaining tissue from the right cornea and globe and with chondroitinase ABC by using tissue from the left globe. There was no further tissue available from Case 2 for the chondroitinase AC experiments.

To test for the systemic mucopolysaccharide disorders, skin fibroblast and white blood cell homogenates from both cases were assayed for the following lysosomal enzymes known to be deficient in clinically relevant mucopolysaccharidoses and mucolipidoses: alpha-L-iduronidase,[29] N-acetylgalactosamine-6-sulfatase,[19] beta-galactosidase,[30] arylsulfatase B,[31] beta-glucuronidase,[32] and arylsulfatase A.[33] Serum from Case 1 and fibroblasts from Cases 1 and 2 were tested for iduronate sulfatase levels.[34] Serum from Case 2 was tested for keratan sulfate level[6] and acid phosphatase level.[35] Urine from Case 2 was tested with acid albumin turbidity[20] and Berry spot[36] screens for urinary mucopolysaccharides.

Results

Light microscopy disclosed, in Cases 1 and 2, deposits throughout all layers of the corneal stroma after staining with alcian blue at pH 0.4 and 2.5 and with colloidal iron (Figs. 3 and 4). Deposits were seen in Bowman's membrane in Case 1 (Fig. 3); Bowman's membrane was not present in Case 2 because of previous lamellar keratoplasty (Fig. 4). There was slight metachromasia with toluidine blue.

Postmortem studies in Case 1 of both the right globe fixed in formalin and the left globe fixed in ethanol disclosed scleral deposits, which had staining properties similar to those in the corneas, positive with alcian blue and colloidal iron and negative with periodic acid-Schiff stain (Fig. 3). An abundant accumulation

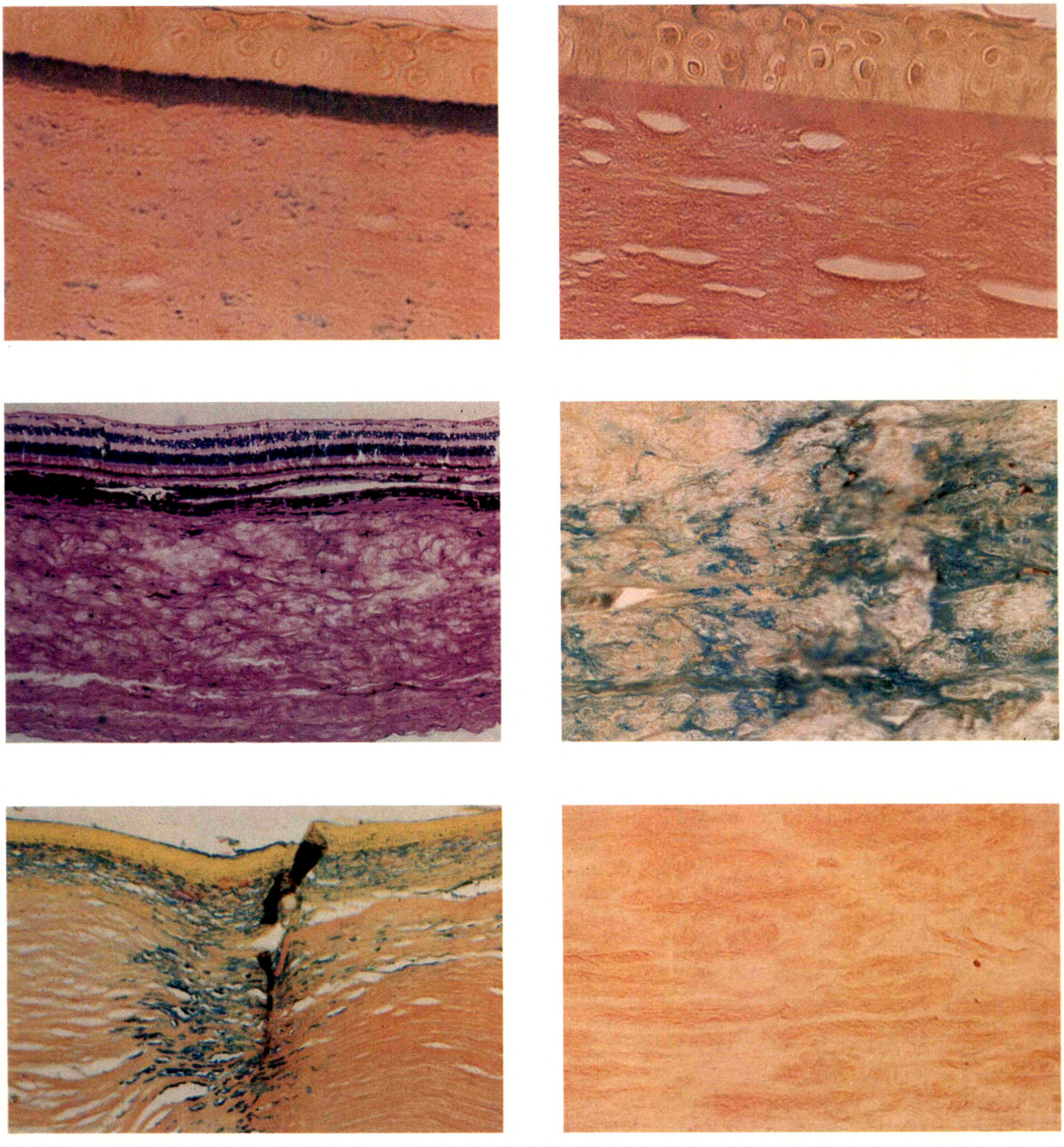

Fig. 3 (Winterbotham and associates). Case 1, right eye. Top left, Colloidal iron preparation of anterior cornea contains abnormal blue staining accumulations in Bowman's membrane and stroma (× 300). Top right, Colloidal iron preparation of anterior cornea after treatment with testicular hyaluronidase shows digestion of blue staining material (× 300). Middle left, Periodic acid-Schiff stain of postmortem sclera shows no deposits (× 200). Middle right, Colloidal iron preparation contains abnormal blue staining accumulations in sclera (× 500) and bottom left, at the graft-host interface more concentrated on host side to left (× 50). Bottom right, Immunohistochemical staining with monoclonal antibody 9-A-2 after treatment with chondroitinase AC in the sclera shows positive brown reaction products (hematoxylin, × 500).

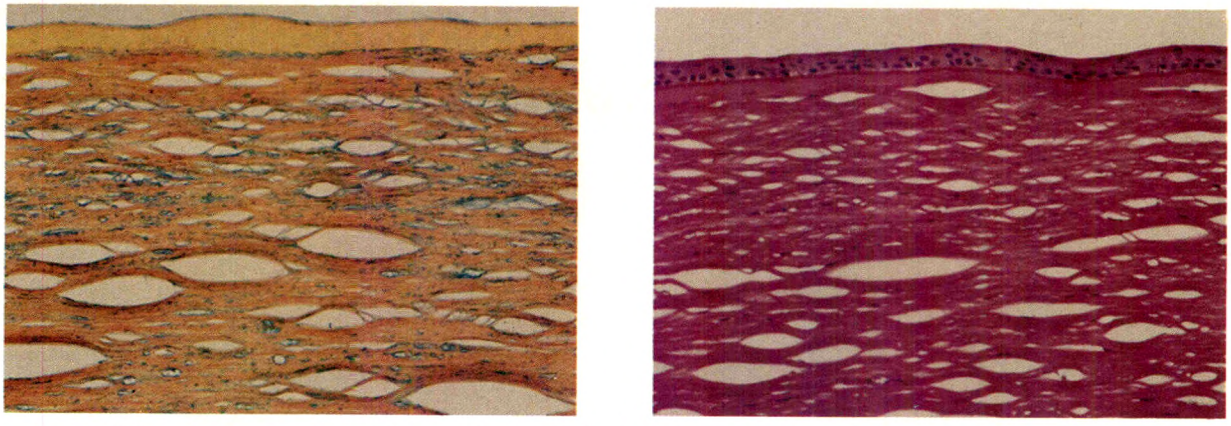

Fig. 4 (Winterbotham and associates). Case 2. Left, Colloidal iron preparation of anterior cornea contains abnormal blue staining deposits (× 125). Right, Deposits not observed with periodic acid-Schiff stain (× 125). A lamellar keratoplasty was performed 14 years before the penetrating keratoplasty sections shown here were obtained.

of such material was observed by colloidal iron staining at the corneal graft-host interface in the right globe of Case 1 (Fig. 3). The interface deposits were extracellular. In Case 2, the scarred area at the site of the original superficial keratectomy did not have an excessive accumulation of the material, but deposits were seen throughout the central stroma (Fig. 4).

There was no reaction with periodic acid-Schiff stain (Figs. 3 and 4) or with hematoxylin and eosin in either case. Staining in Case 1 with Masson trichrome, Congo red, mucicarmine, and Prussian blue showed no reaction. Cryostat sections of the formalin-fixed cornea in Case 1 did not react with Sudan black, oil red O, and Schultz's cholesterol method.

Preliminary results of testing with *Streptomyces* hyaluronidase and chondroitinase ABC and AC showed apparent resistance of the material,[37] but testicular hyaluronidase completely digested the material. Repeat testing for sensitivity to both chondroitinase ABC and AC in corneal and whole globe sections from Case 1 showed that there was indeed digestion of colloidal iron-positive material in the cornea and sclera. Parallel experiments using fresh-frozen cartilage and dermis as positive controls showed complete digestion of colloidal iron-stainable material, as would be expected. Chondroitinase ABC digested corneal material in Case 2. Immunohistochemical staining indicated binding of the 9-A-2 monoclonal antibody after treatment with chondroitinase ABC in the corneas of both cases (Fig. 5) and after chondroitinase AC in the cornea and sclera of Case 1 (Figs. 3 and 5). There was no tissue available in Case 2 for experiments with chondroitinase AC.

Because there was no extraocular tissue available to complete enzyme studies, the extraocular sections stained with periodic acid-Schiff stain and hematoxylin and eosin were examined by pathologists who specialize in diseases of the heart, liver, and kidney to check for evidence of storage disease. The kidney sections showed progressive nephrosclerosis; the liver sections showed chronic passive congestion; and the heart sections disclosed focal ischemic fibrosis. Abnormal storage material was not observed in these tissues, nor in the spleen, aorta, or lungs.

Electron microscopic study of the corneas from both cases showed nonmembrane-bound vacuoles of various sizes interspersed throughout the corneal stroma between the lamellae (Figs. 6 and 7) and rarely in the keratocytes (Fig. 7). In the vacuoles, condensation of material produced black circular profiles that appeared retracted from the edge of the vacuole, occasionally with granular material within the profile. Fine vacuoles were densely dispersed throughout Bowman's membrane (Fig. 8). The epithelium, Descemet's membrane, and the endothelium were normal. Collagen arrangement was normal.

Enzyme assays of white blood cell and skin fibroblast extracts from both cases showed normal levels of the mucopolysaccharidosis-related enzymes: alpha-L-iduronidase (MPS I, Hurler/Scheie), N-acetylgalactosamine-6-sulfatase (MPS IVA, Morquio), beta-galactosidase (MPS IVB, Morquio), arylsulfatase B (MPS VI,

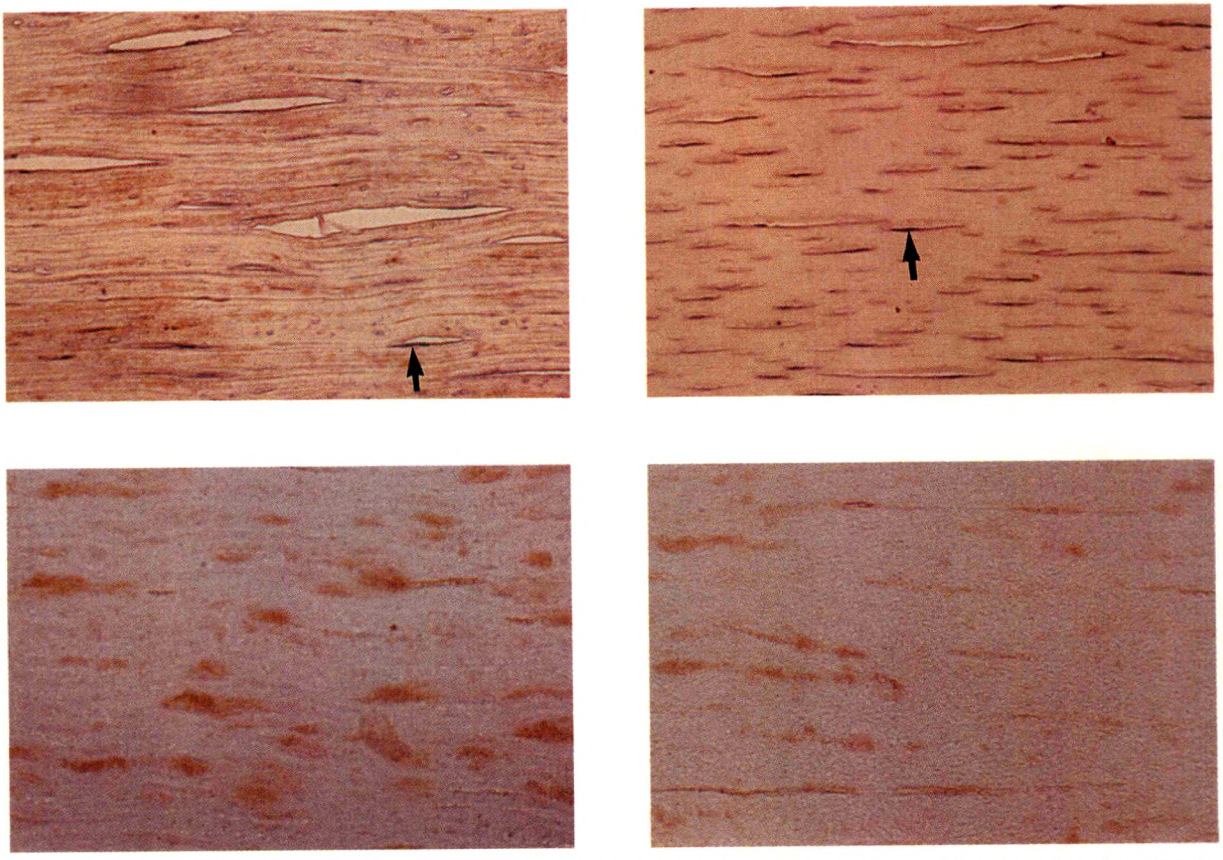

Fig. 5 (Winterbotham and associates). Top left, Immunohistochemical staining with monoclonal antibody 9-A-2, after treatment of the posterior cornea of Case 2 with chondroitinase ABC, discloses diffuse brown reaction products in the stroma (hematoxylin, × 200). Top right, Reaction products not present in a normal human control section (hematoxylin, × 200). There is a counterstain artifact in keratocytes (arrows) of both Case 2 and control. Bottom left, Using monoclonal antibody 9-A-2 in the cornea of Case 1, the stroma contains positive brown reaction products after treatment with chondroitinase ABC (hematoxylin, × 500) or, bottom right, chondroitinase AC (hematoxylin, × 500).

Maroteaux-Lamy), and beta-glucuronidase (MPS VII, Sly) (Tables 1 and 2). Normal levels of arylsulfatase A and beta-galactosidase helped rule out the mucolipidoses (Tables 1 and 2). The controls run at the same time were within the normal range. The serum level of iduronate sulfatase (MPS II, Hunter) from Case 1 was lower than the control level and the normal range for our laboratory; the fibroblast level was higher than that of the control, but near the high end of the normal range. Although below the normal range for this laboratory, the serum level in Case 1 was well above the lowest serum value diagnostic of Hunter disease, which is 0.08 ± 0.03 nmol/mg/hr.[34] Even though the serum assay has been described as the method of choice,[34] serum levels may fluctuate in the presence of other medical conditions, such as the renal failure in Case 1. The cellular levels (in skin fibroblasts for iduronate sulfatase, or skin fibroblasts and white blood cells for the other enzyme assays) are expected to be more representative of the actual value. The serum level in Case 1 appears to be spuriously low. Serum for the iduronate sulfatase assay was not available from Case 2, but the fibroblast level was normal (Tables 1 and 2). In Case 2, the serum level of keratan sulfate was 309 ng/ml (normal mean, 268 ng/ml), the serum acid phosphatase level was 10.1 I.U. (normal range, 2.0 to 9.4 I.U.), and urine acid albumin turbidity and Berry spot screens for mucopolysaccharide were negative. Patient 1 died before serum keratan sulfate and acid phosphatase assays and urine screens could be performed.

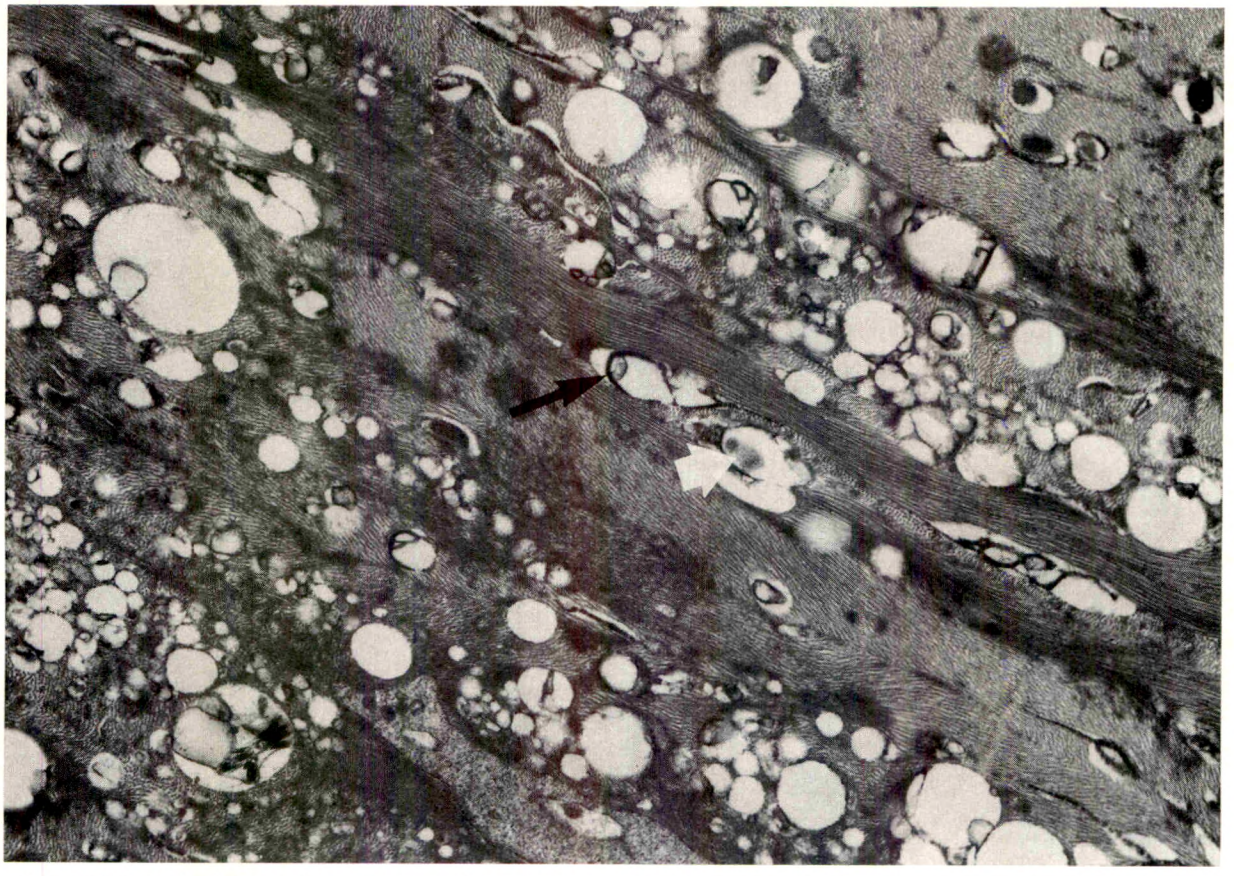

Fig. 6 (Winterbotham and associates). Case 1. Electron micrograph of corneal stroma with nonmembrane-bound vacuoles located between the lamellae. Black circular profiles retracted from the edge of the vacuoles (black arrow) occasionally contain granular material (white arrow) (× 10,000).

Discussion

The deposits found in the corneas of two patients and the postmortem sclera of one patient contained the glycosaminoglycans chondroitin 4-sulfate and dermatan sulfate. Deposition of these glycosaminoglycans, or the proteoglycans of which they are a part, is clinically significant because their distribution affects corneal transparency. Normal distribution maintains the structural integrity of the extracellular matrix.[3-5,21,22,26,28] Various conditions that cause a change in proteoglycans can disrupt the collagen arrangement. Using corneal wound healing as a model, the orderly packing of collagen fibrils is disorganized when synthesis of different (or excess) glycosaminoglycans causes enlargement of the interfibrillar spacing.[5] Increased chondroitin sulfate has been reported in corneal scar tissue and increased dermatan sulfate in nontransparent corneal grafts.[4,21] We postulate that the excess chondroitin sulfate or dermatan sulfate in our cases caused the disarray of the extracellular stromal matrix, causing corneal opacification.

We identified the material in the cases based on the following results. The positive reaction with the cationic dyes alcian blue, colloidal iron, and toluidine blue disclosed the presence of glycosaminoglycan-like molecules,[1,4,11-13,16] such as chondroitin sulfate, dermatan sulfate, hyaluronic acid, or keratan sulfate. Negative reaction with periodic acid-Schiff stain indicated that the material was not keratan sulfate, which lacks the uronic acid common in other glycosaminoglycans.[4] Chondroitin sulfate and dermatan sulfate were positively identified through digestion of the deposits by enzymes known to degrade these two glycosaminoglycans. Digestion by testicular hyaluronidase in both cases suggested the presence of chondroi-

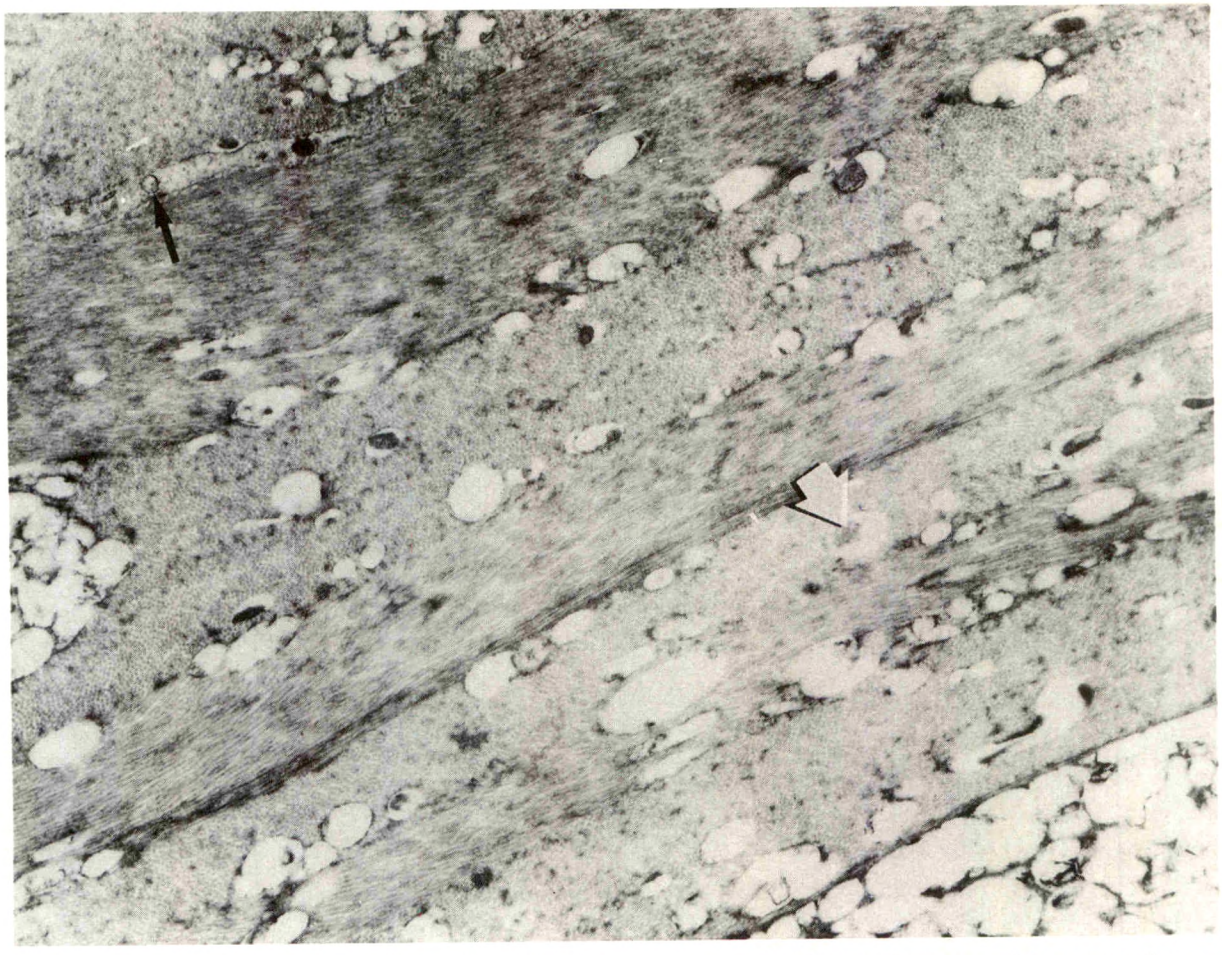

Fig. 7 (Winterbotham and associates). Case 2. Electron micrograph of corneal stroma with nonmembrane-bound vacuoles and granular material (white arrow) similar to findings in Case 1. Vacuoles in both cases are largely extracellular. A rare vacuole is observed in a keratocyte (black arrow) (× 10,000).

tin 4- and 6-sulfates.[4] Chondroitinase ABC digested the material in both cases, indicating the presence of chondroitin 4- or 6-sulfate and dermatan sulfate.[5,22,23,25-27] Chondroitinase AC digestion in Case 1 supported the presence of chondroitin 4- or 6-sulfate, but not dermatan sulfate, because chondroitinase AC does not digest dermatan sulfate.[25,26] Hyaluronic acid could have also been present, because it is degraded by testicular hyaluronidase,[4] chondroitinase AC,[25,26] and slightly by chondroitinase ABC at pH 8.0,[23] the pH at which the enzyme was tested in our experiments.

The monoclonal antibody staining confirmed the type of glycosaminoglycan suggested by enzyme digestion. Digestion by chondroitinase ABC or AC leaves a residual delta-unsaturated disaccharide with sites available for monoclonal antibody 9-A-2 binding.[26,27] Binding by the 9-A-2 antibody after chondroitinase ABC degradation of the glycosaminoglycan-containing material identified chondroitin 4-sulfate or dermatan sulfate or both in Cases 1 and 2.[26,27] The antibody recognizes the disaccharide whether it is from chondroitin 4-sulfate or dermatan sulfate.[27] Binding of 9-A-2 after chondroitinase AC digestion in Case 1 more specifically identified chondroitin 4-sulfate because chondroitinase AC does not degrade dermatan sulfate.[25,26] Because 9-A-2 staining yielded similar intensity after digestion by both chondroitinase AC and ABC in Case 1, we concluded that chondroitin 4-sulfate was the predominant component, rather than dermatan sulfate or both equally. The 9-A-2 antibody does not react with hyaluronic acid.[26,27]

Our results did not eliminate the possibility of the presence of substances in addition to

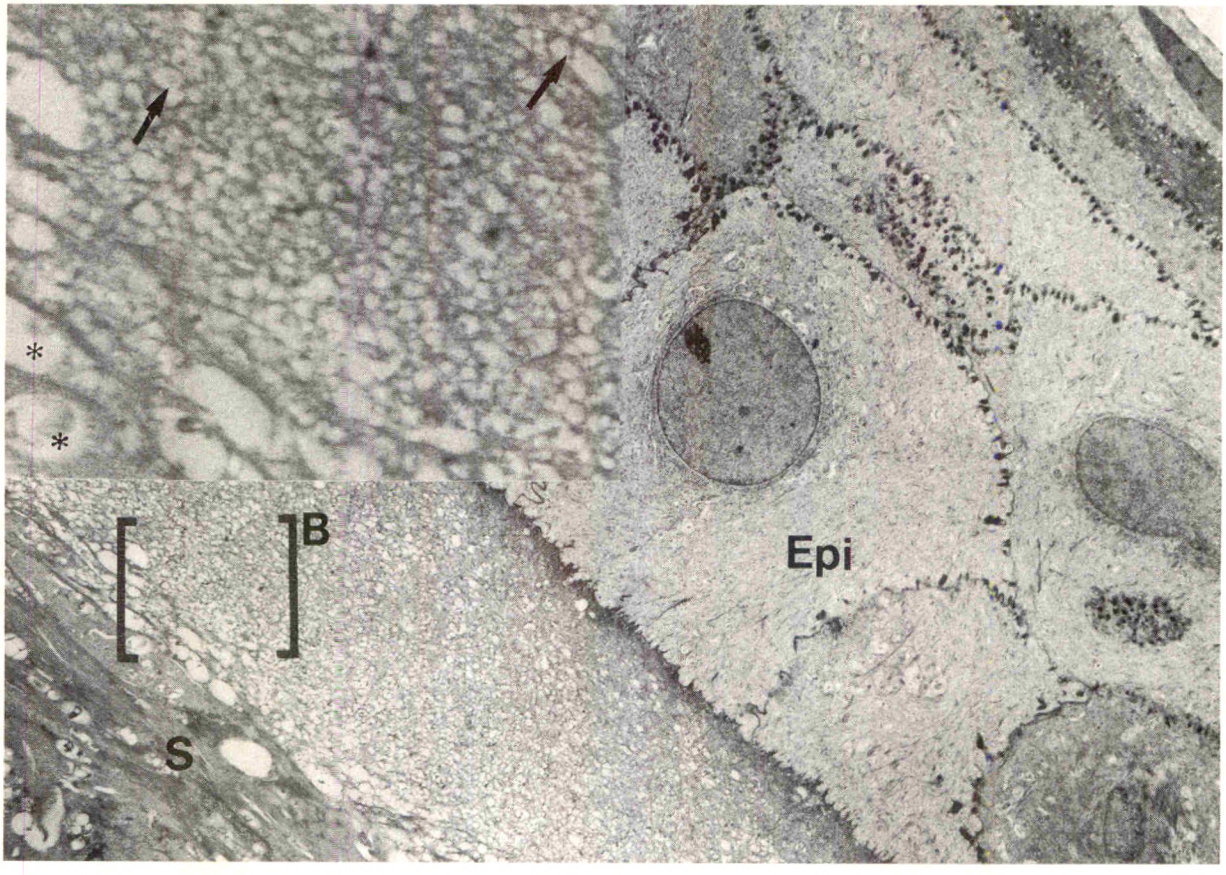

Fig. 8 (Winterbotham and associates). Case 1. Electron micrograph of epithelium (Epi), Bowman's membrane (B), and anterior stroma (S). Bowman's membrane is packed with small vacuoles more concentrated posteriorly. The epithelium is unremarkable (× 8,000). Inset (taken from bracketed area), Vacuoles in Bowman's membrane contain granular material (arrows) similar to material in stromal vacuoles (asterisks) (× 32,000).

TABLE 1
RESULTS OF ENZYME ASSAYS ON BLOOD*

ENZYME	CASE 1	CONTROL	CASE 2	CONTROL	NORMAL RANGE
α-L-Iduronidase (nmol/mg/hr)	4.66	3.98	4.30	3.56	2.50–6.60
Iduronate sulfatase (nmol/mg/hr)†	24.6	103.1	ND	ND	81.8–163.2
N-acetylgalactosamine-6-sulfatase (nmol/mg/hr)	5.77	3.15	8.50	7.98	3.10–14.80
β-galactosidase (μmol/mg/hr)	0.087	0.117	0.118	0.076	0.065–0.120
Arylsulfatase B (μmol/mg/hr)	0.265	0.142	0.100	0.056	0.084–0.200
β-glucuronidase (μmol/mg/hr)	0.503	0.428	0.594	0.307	0.300–0.600
Arylsulfatase A (μmol/mg/hr)	0.087	0.081	0.086	0.073	0.070–0.110

*Assays were performed on whole sonicates of leukocytes except for the iduronate sulfatase assay performed on serum. Samples from Cases 1 and 2 were largely assayed in separate experiments. In each experiment, "Control" represents normal cells or serum assayed in parallel. Normal ranges are from the University of Chicago lysosomal storage disease laboratories. Serum value for iduronate sulfatase in Case 1, though below the normal range and control for this laboratory, is still within normal limits.

†ND indicates not determined.

TABLE 2
RESULTS OF ENZYME ASSAYS ON FIBROBLASTS*

ENZYME	CASE 1	CONTROL	CASE 2	CONTROL	NORMAL RANGE
α-L-Iduronidase (nmol/mg/hr)	19.28	21.06	20.87	21.06	19.3–35.0
Iduronate sulfatase (nmol/mg/hr)	24.30	5.59	3.68	5.59	2.90–21.80
N-acetylgalactosamine-6-sulfatase (nmol/mg/hr)	10.32	6.55	6.79	6.58	4.90–11.70
β-galactosidase (μmol/mg/hr)	0.297	0.350	0.501	0.350	0.240–0.650
Arylsulfatase B (μmol/mg/hr)	0.427	0.157	0.285	0.157	0.150–0.350
β-glucuronidase (μmol/mg/hr)	0.518	0.235	0.215	0.235	0.215–0.520
Arylsulfatase A (μmol/mg/hr)	0.450	0.452	0.838	0.381	0.400–1.100

*Assays were performed on whole sonicates of fibroblasts. Samples from Cases 1 and 2 were largely assayed in separate experiments. In each experiment, "Control" represents normal cells assayed in parallel. Normal ranges are from the University of Chicago lysosomal storage disease laboratories.

chondroitin 4-sulfate and dermatan sulfate but identified the important components. Although monoclonal 9-A-2 antibody binding does not define the core protein of the proteoglycan or the remainder of the glycosaminoglycan chain beyond the disaccharides at the linkage region,[22,26] the binding did help reduce the significance of glycosaminoglycans with which the antibody does not react, such as hyaluronic acid. We were able to exclude other substances such as collagen, hyaline, amyloid, and lipid because the deposits did not stain with hematoxylin and eosin, Masson trichrome, Congo red, mucicarmine, Prussian blue, the cholesterol method, oil red O, or Sudan black.

We compared our findings to those in diseases involving localized glycosaminoglycan (mucopolysaccharide) deposition in the corneal stroma and found differences. Looking first at reported cases of unknown cause, mucopolysaccharide deposits in Bowman's membrane of two neonates were resistant to hyaluronidase,[12] and deposits in Bowman's membrane and the extracellular stroma of a 20-year-old woman were reactive with periodic acid-Schiff stain, unlike those in our cases.[13] Stromal deposits in fleck corneal dystrophy are located intracellularly, not extracellularly; fleck dystrophy involves lipid deposition, as well as glycosaminoglycan deposition, and is clinically not like our cases, despite the slight similarity of the vacuoles on electron microscopic examination.[4,9,11]

Several systemic diseases have vacuoles that appear similar to the vacuoles in our cases on electron microscopy, but there are significant differences. Lecithin cholesterol acyltransferase deficiency, despite its ring of peripheral corneal deposits that do not react with histochemical stains for fats, is a disorder of lipid metabolism and does not involve glycosaminoglycan deposition.[9,11,38] The mucolipidoses do have glycosaminoglycan deposition but also have systemic lipid manifestations.[9-11]

The systemic mucopolysaccharidoses involve glycosaminoglycan deposition similar to that in our cases. As in our cases, there is storage of glycosaminoglycans in Bowman's membrane and the intracellular and extracellular corneal stroma with Descemet's membrane spared.[4,9-13,16-20] Excess chondroitin sulfate is deposited in types IV, VI, and VII and dermatan sulfate in types I, II, VI, and VII.[9] Type VI (Maroteaux-Lamy) bears the most resemblance to our cases with both dermatan sulfate and chondroitin 4-sulfate stored,[9] thickening of the sclera (also in type II),[4] and recurrence at the graft-host interface after penetrating keratoplasty.[9,17] Unlike in our cases, deposits in the mucopolysaccharidoses are found in the corneal epithelium and endothelium and systemically.[4,9-13,16-20] Results of lysosomal enzyme assays were normal in our cases (Tables 1 and 2), helping rule out the pertinent mucopolysaccharidoses and mucolipidoses.

Macular corneal dystrophy also has similarities to our cases, including extracellular stromal deposits, their structure on electron microscopy,[1,4,9,11-13] and the recurrence of the material at the graft-host interface after both lamellar and penetrating keratoplasty.[1,4,8,14,15] Unlike those in our cases, the opacities observed clinically appear more concentrated in the central stroma and are present in corneal endothelium and Descemet's membrane.[1,4,7-14,16] The excess gly-

cosaminoglycan is an abnormal keratan sulfate moiety[2-9,11,14,15] that is reactive to periodic acid-Schiff stain[1,2,4,7,9,11] and resistant to testicular hyaluronidase and chondroitinase ABC and AC.[1,4,9,11,14] Macular corneal dystrophy is a heterogeneous disease[2,6-8] recently found to be systemic.[6-8] Previously, the disease was considered to be restricted to the cornea, except in one case reported where there was conjunctival involvement possibly caused by a diffusion-like process from the cornea.[16] Perhaps a diffusion-like process could explain the scleral deposits in Case 1. The mechanism could be similar to one proposed for recurrence in macular corneal dystrophy in which there may be direct penetration of the abnormal glycosaminoglycan into donor tissue[15] rather than keratocyte migration.[14,15,17] The question raised is whether the scleral deposits could signify a systemic problem. Despite the presence of deposits in the sclera and the preponderance of extracellular stromal material, we cannot define the disease as systemic in our cases. Examination of postmortem extraocular tissue in Case 1 did not disclose storage of excess glycosaminoglycans, and the results of the skin fibroblast and blood lysosomal enzyme assays were normal in both cases.

Exploring the source of the corneal and scleral material raises further questions about the disorder's pathogenesis. One possible cause could be the overproduction of the glycosaminoglycans in our cases. This mechanism has been suggested for the excess of hyaluronic acid in Marfan's syndrome,[39] but there are no other known cases. Another cause of the disorder could be an abnormal biosynthetic enzyme similar to the possibly defective sulfotransferase suggested in macular corneal dystrophy.[3] The abnormal glycosaminoglycan produced by the defective enzyme would then not have been recognized by normal degradative enzymes. A likely alternative is that there was a defective degradative enzyme different from the lysosomal enzymes usually deficient in mucopolysaccharide disorders. The enzyme could be nonlysosomal and possibly restricted to the cornea, resulting in extracellular stromal accumulation. Speculation about abnormal or deficient enzymes raises questions about inheritance patterns; we can make no conclusions about such patterns because Patient 1 had only one known aunt with corneal opacities and Patient 2 had a noncontributory family history.

Further definition of the unusual glycosaminoglycan (mucopolysaccharide) disorder will depend on the description of new cases as well as follow-up analysis of material from the cases described herein. Studies on the metabolism of complex carbohydrates in the cells of these patients may lead to the biochemical basis for the glycosaminoglycan accumulations.

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Progressive Visual Field Defects in Patients With Intracranial Arteriovenous Malformations

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Two men, aged 59 and 36 years, had large, intracranial arteriovenous malformations. Both patients developed severe, bilateral visual loss secondary to unrecognized chronic papilledema. Lumbar puncture disclosed increased intracranial pressure. Neuroimaging disclosed only vascular malformations. The patients were treated by embolization of the vascular malformations and ventriculoperitoneal shunting procedures. The malformation of one patient was excised.

THE LACK of consistent correlation between the clinical features and the size, location, and vascular patterns of intracranial arteriovenous malformations is well known.[1] This lack of correlation has been related to the congenital nature of the malformation and to the mechanisms by which symptoms may be produced, such as hemorrhage or mass effect.[1-3] Visual field loss in arteriovenous malformations is a well-known sequela of increased intracranial pressure secondary to hemorrhage, hematoma, or obstructive hydrocephalus.[1,4] We treated two patients who had severe visual field loss secondary to chronic papilledema attributable to increased intracranial pressure.

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Case Reports

Case 1

A 59-year-old right-handed man complained of severe visual loss in March 1988. In January 1976, he had a syncopal episode associated with nausea, vomiting, and general malaise. A brain scan performed at that time reportedly showed increased uptake in the right posterior temporal lobe area. Cerebral angiography showed a dural and tentorial arteriovenous malformation with deep extension. Results of neurologic evaluation were normal. The optic disks were normal.

No definitive treatment was recommended. The patient was lost to follow-up until May 1980, at which time the patient had a generalized tonic-clonic seizure associated with a one- to two-minute episode of loss of consciousness. A diagnosis of temporal lobe seizures secondary to the arteriovenous malformation was made. The presence and size of the arteriovenous malformation were confirmed again by cerebral angiography. The patient was treated with phenytoin (400 mg/day) to control the seizure activity.

The patient did not seek further medical attention until August 1985 when he complained of difficulty seeing. Neurologic evaluation disclosed blurring of the nasal margins of the optic disk in the right eye and elevation of the disk margin 360 degrees in the left eye. The results of the remainder of the neurologic evaluation were noncontributory. A computed tomographic scan performed in March 1986 disclosed a large arteriovenous malformation that involved much of the right temporal, parietal, and occipital lobes.

The patient was first examined by an ophthalmologist in February 1989 for decreased vision in his right eye of several months' duration. Pertinent findings on examination included a

visual acuity of R.E.: counting fingers at two feet and L.E.: 20/50. Both pupils reacted to light, although the reaction of the right pupil was sluggish. A relative afferent pupillary defect was present on the right side. Ophthalmoscopic examination of the right eye disclosed optic atrophy with blurring of the disk margin nasally, sheathing of vessels at the 5:00 o'clock meridian with arteriolar narrowing, and absence of spontaneous venous pulsations. The margins of the left disk were blurred for 360 degrees, and a small refractile body was present at the disk border at the 6:00 o'clock meridian. There were no spontaneous venous pulsations. Kinetic visual fields performed with a Goldmann perimeter disclosed a temporal island in the right eye only and large superior and temporal defects in the left eye (Fig. 1).

The patient was admitted to our institution for further examination and treatment. A four-vessel angiogram confirmed the presence of a large arteriovenous malformation along the edge of the tentorium predominantly on the right side (Fig. 2). The main arterial supply came from branches of the external carotid artery, including the middle meningeal artery, the internal maxillary artery, and the suboccipital artery. Some branches from the vertebral artery and middle cerebral artery also supplied blood to the malformation. Venous drainage occurred through the straight sinus and the sigmoid sinus by means of multiple collateral vessels. Embolization of the malformation was performed by using both the right external carotid and the right middle meningeal arteries.

On the basis of the presence of chronic disk edema with significant visual field loss, the neuro-ophthalmological service requested that the patient undergo a lumbar puncture. The neurosurgical service was uncertain about the indications for this procedure, but acquiesced, and a lumbar puncture was performed. The opening pressure was 480 mm H_2O. A ventriculoperitoneal shunting procedure was then performed to decompress the patient's optic nerves. The patient's visual function test results remained unchanged after surgery, but ophthalmoscopic examination showed decreased papilledema in his left eye and spontaneous venous pulsations. The patient was seen again in May 1988, at which time there was minimal further loss of temporal field in the right eye and constriction of the inferior nasal field in the left eye. Repeat lumbar puncture was recommended but refused.

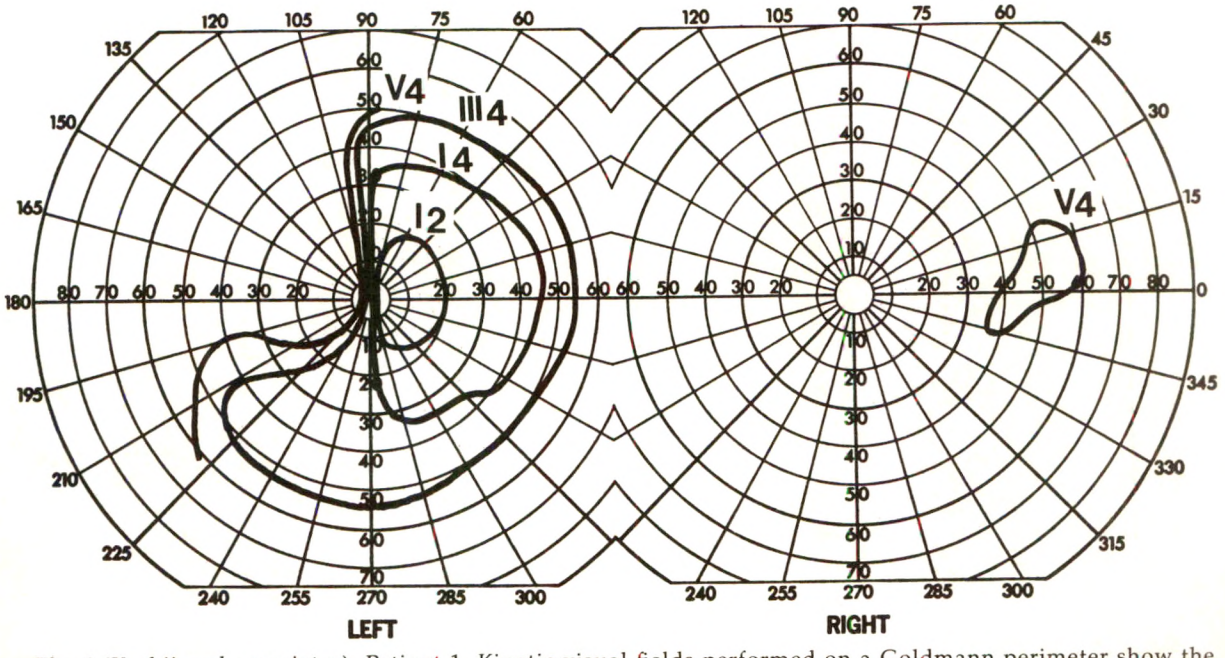

Fig. 1 (Kashii and associates). Patient 1. Kinetic visual fields performed on a Goldmann perimeter show the superior temporal field defect in the left eye associated with a significant visual field defect in the right eye, which fits the definition of "junctional scotoma."

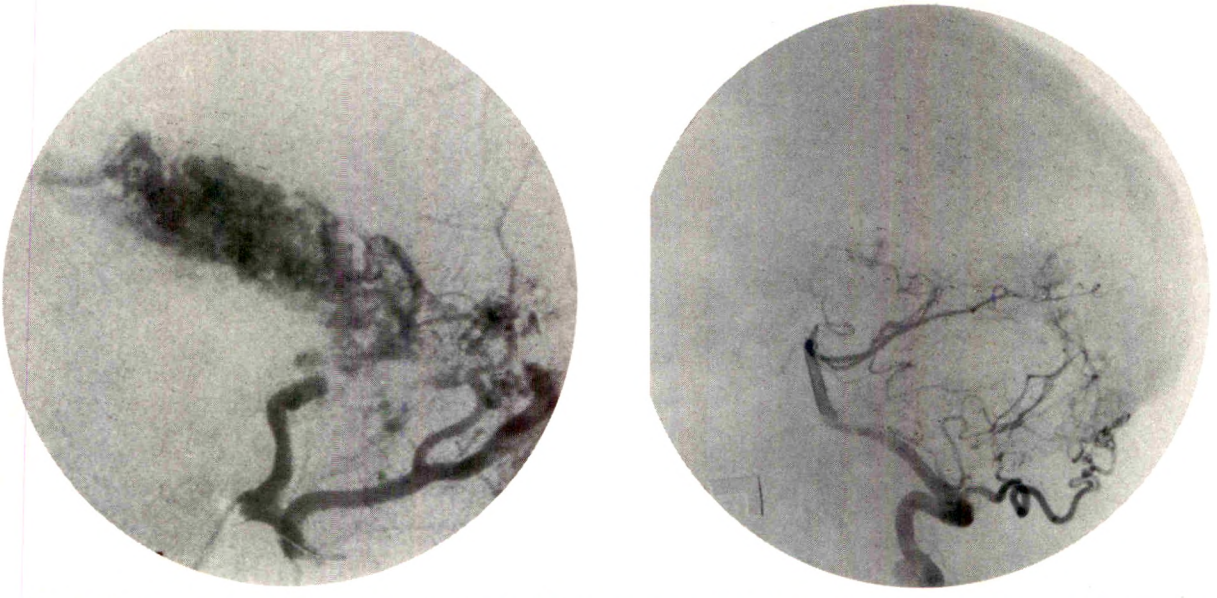

Fig. 2 (Kashii and associates). Patient 1. Left, Selective angiogram shows dural arteriovenous malformation developing from right meningeal artery. Right, Left vertebral angiogram shows emissary artery feeding dural arteriovenous malformation from muscular branches of left vertebral artery.

Case 2

A 36-year-old right-handed man with a known intracranial arteriovenous malformation that was diagnosed in 1981 was examined in March 1988 for a progressive visual field loss in both eyes. In 1981, the patient began to have generalized tonic-clonic seizures. At that time, examination included an electroencephalogram, a computed tomographic scan, and an angiogram, which showed the presence of a large, right parietal arteriovenous malformation.

The patient first noted a problem with his vision in 1985, at which time he complained of decreased vision in his left eye. The only afferent visual system finding was bilateral papilledema. No visual field testing was performed. A computed tomographic scan again confirmed the presence of a right parietotemporal arteriovenous malformation with large feeding channels, and it was presumed that the chronic disk edema was caused by a mass effect.

The patient was lost to follow-up until February 1986, at which time neuro-ophthalmologic examination disclosed a visual acuity of R.E.: 20/30 and L.E.: hand motions. Ophthalmoscopic examination showed evidence of severe optic atrophy without disk elevation. The patient was lost to follow-up again until March 1988, at which time he returned because of severe visual difficulties. Complete ophthalmic examination at that time disclosed a visual acuity of R.E.: 20/25 and L.E.: light perception superonasally. The pupils were 4 mm and 5 mm on the right and left, respectively, and reacted sluggishly to direct light stimulation at 3 mm and 4 mm, respectively. There was a markedly positive relative afferent pupillary defect on the left side. On ophthalmoscopic examination, the optic disks were pale and flat with sharp margins. There was no evidence of edema, hemorrhage, or infarction. Kinetic visual fields done both on a tangent screen at 1, 2, and 3 m and on a Goldmann perimeter disclosed a small, centrally skewed island of vision (Fig. 3).

On the basis of optic atrophy and history of papilledema, lumbar puncture was recommended. The neurosurgical service acquiesced again, and the opening pressure was 310 mm H_2O. A computed tomographic scan did not differ significantly from the one done in 1985. A cerebral angiogram showed slow filling of a large, right frontoparietal arteriovenous malformation through feeders mainly from the right middle cerebral artery and, to a lesser degree, from the right posterior cerebral artery and the right anterior cerebral artery. The malformation was drained by two large, superficial, cortical veins that emptied into the superior sagittal sinus.

A ventriculoperitoneal shunt procedure was performed (Fig. 4). Embolization therapy was

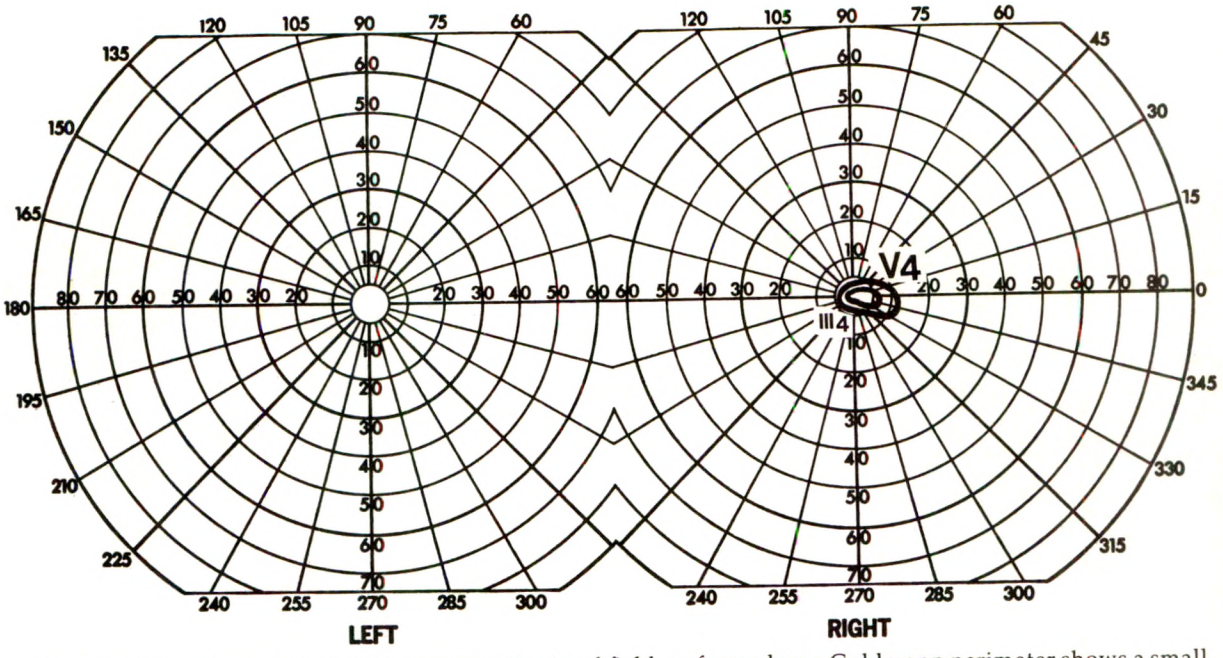

Fig. 3 (Kashii and associates). Patient 2. Kinetic visual field performed on a Goldmann perimeter shows a small, 5-degree central island slightly skewed temporally. The visual acuity of the left eye is light perception.

subsequently initiated, followed by a craniotomy with partial removal of the arteriovenous malformation. The visual field remained unchanged. In June 1986, the patient underwent removal of the residual tumor.

Immediately after surgery, the patient complained of loss of vision in his right eye. A computed tomographic scan showed a large, hypodense, extra-axial collection under the right craniotomy flap with ventricular efface-

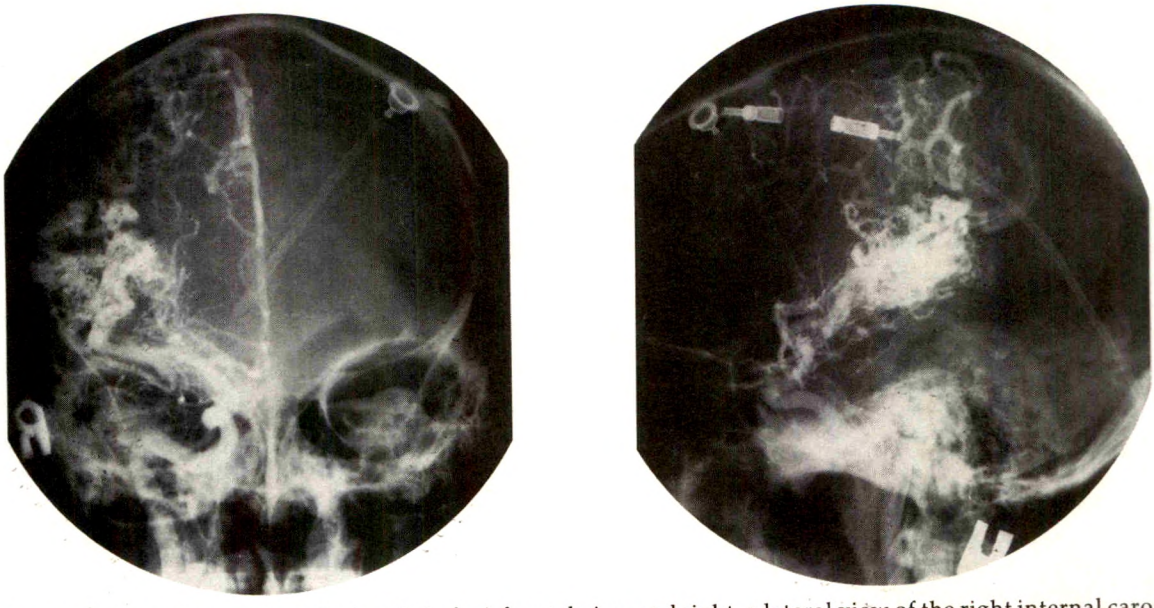

Fig. 4 (Kashii and associates). Patient 2. Left, A frontal view and right, a lateral view of the right internal carotid arteriogram show the large arteriovenous malformation located mainly in the parietal region. The malformation is fed from the right middle cerebral artery. The ventriculoperitoneal shunt cannula can be seen in the right lateral ventricle.

ment and compression. After drainage by means of a twist drill, the patient's vision returned to its preoperative state.

Discussion

Both of our patients lost visual function because of the unrecognized consequences of chronic papilledema secondary to raised intracranial pressure. Evidence of chronic papilledema was present in Patient 1, whereas Patient 2 had advanced optic atrophy with a history of papilledema and a lumbar puncture that confirmed the presence of increased intracranial pressure. Papilledema and raised intracranial pressure are unusual signs of a cerebral arteriovenous malformation in the absence of severe secondary intracranial hemorrhage or hematoma, unless the arteriovenous malformation is huge. In 110 patients with cerebral arteriovenous malformation, Paterson and McKissock[2] found only one patient who had papilledema without a specific cause.

Intracranial arteriovenous malformations have been classified angiographically on the basis of their arterial supply as purely dural, mixed dural and pial, and purely pial.[5] Pure dural malformations are limited to the dura and receive only meningeal arterial blood. Mixed dural and pial malformations receive their blood supply not only from meningeal vessels but also from cerebral or cerebellar arteries. Purely pial malformations are intracranial lesions that are supplied only by cerebral or cerebellar arteries, without meningeal contribution.

Dural arteriovenous malformations are generally rare. They comprise 6% to 12% of intracranial arteriovenous malformations[5,6] and occur predominantly in women over 40 years of age.[7] Dural malformations in the posterior fossa are far more common than are those above the tentorium. Of the supratentorial arteriovenous malformations in one study, only 6% were dural, but of the infratentorial malformations, 35% were dural.[5] The malformation of Patient 1 is classified as mixed dural-pial because of its arterial supply. It is, however, more predominantly of the dural type, because most of its blood supply is derived from dural vessels.

As early as 1968, dural arteriovenous malformations that developed in the posterior fossa were regarded as a distinct entity because of their frequent association with pseudotumor-like symptoms.[8,9] In two studies, 14% to 24% of patients with dural malformations involving the transverse sinus were reported to have papilledema,[10,11] but the authors included patients in whom hydrocephalus or subarachnoid hemorrhage also existed. Recently, Houser and associates[12] reported that five of 14 of their patients with dural arteriovenous malformations that affected the transverse sinus had increased intracranial pressure and no history of subarachnoid hemorrhage or hydrocephalus. The investigators postulated that dural sinus occlusion precedes the development of dural arteriovenous malformations in the transverse sinus.

Most posterior fossa dural malformations develop within or in direct proximity to a major venous sinus. These malformations raise the venous pressure by direct shunting of arterial blood,[11,13] and this is believed to be the primary cause of papilledema in dural arteriovenous malformations in the posterior fossa.[14-16]

Pial arteriovenous malformations are the most common intracranial arteriovenous malformations (72%).[5] They affect men slightly more often than they affect women.[17,18] They are associated with the triad of hemorrhage, seizures, and recurrent headaches.[19] Chronic increased intracranial pressure without a history of either intracranial hemorrhage or hydrocephalus, however, is rare in pial malformations.[2,20-23] The difference in inducing raised intracranial pressure between dural and pial malformations appears to be attributable to the direct drainage of the enlarged dural arteries into involved sinuses. This produces a rise in venous pressure in dural malformations, whereas pial malformations rarely shunt directly into the dural sinuses[24]; rather they increase venous pressure because of the massive runoff from large shunting vessels, which produces increased cerebral blood volume and decreased cerebrospinal fluid absorption.[14,20,22,23,25,26] Both of our patients had pial malformations functionally. The malformation of Patient 1 could, on the basis of the origin of its blood supply, be classified as a dural malformation, but it did not directly shunt blood into the venous sinuses. Thus, the finding of increased intracranial pressure suggests that the malformation is acting as though it were pial.

Increased intracranial pressure has been long known to cause bilateral papilledema. Only rarely has it been recognized that asymmetric papilledema may occasionally be seen in patients with pseudotumor cerebri, especially at initial examination.[27-30] Based on the presence of

a relative afferent pupillary defect, one study of a large series of patients with pseudotumor cerebri estimated that asymmetric visual field defects were seen in 16 of 59 (28%) patients.[27] In our Patient 1, the left eye had a superotemporal field defect that respected the vertical meridian, whereas only a temporal island of vision remained in the right eye. Although the loss of the left homonymous field in both eyes is explained on the basis of the location and size of the arteriovenous malformation, the remainder of loss of visual function is most likely attributable to field loss associated with the optic atrophy of chronic disk edema.

Decreased vision in one eye with a superotemporal field defect in the fellow eye suggests a junctional scotoma. There is no visible mass effect, however, in the region of the right prechiasmal optic nerve as reaffirmed by multiple neuroradiologic examinations, including magnetic resonance imaging (Fig. 5). It is possible that the asymmetry seen may be attributable to a steal phenomenon from the ophthalmic artery to the arteriovenous malformation.

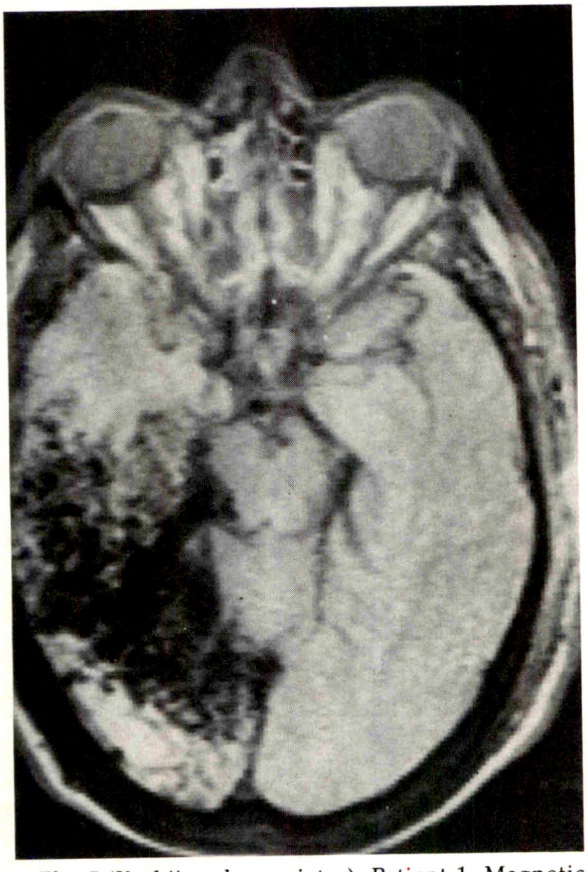

Fig. 5 (Kashii and associates). Patient 1. Magnetic resonance image, T_2-weighted, shows a large, brighter (hyperdense) area that corresponds to the parietotemporal arteriovenous malformation. There is no visible mass in the right prechiasmal region. (Left is the patient's right, and right is the patient's left.)

In Patient 2, the observation of bilateral papilledema early in the course of the process, which is documented in his old record, leads us to postulate that there must have been intermittent increases in intracranial pressure that eventually produced almost total loss of axons. This loss of axons precluded the development of disk elevation even with a substantiated increase in intracranial pressure at the time of our observation.

The clinician should be aware of this infrequent cause of papilledema. Intracranial arteriovenous malformations, whether dural or pial in type, can produce an asymptomatic chronic increase of intracranial pressure. Treatment should be aimed primarily at the underlying arteriovenous malformation. The associated development of chronic papilledema can produce progressive visual loss; patients with papilledema, like those with pseudotumor cerebri, must have sequential visual field testing on a regular basis. If progressive loss of visual field is documented over one to four weeks, a shunting procedure or an optic nerve sheath fenestration should be performed.

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Safety of Fluorescein Angiography During Pregnancy

Lawrence S. Halperin, M.D., R. Joseph Olk, M.D., Gisele Soubrane, M.D., and Gabriel Coscas, M.D.

We sent 424 retina specialists questionnaires on fluorescein angiography performed on pregnant women; 399 specialists responded. Of these, 309 (77%) had never performed fluorescein angiography on a pregnant woman. Ninety specialists (23%) had performed at least one fluorescein angiogram on a pregnant woman; detailed information was obtained on 105 patients. Authors of previous reports that included fluorescein angiography during pregnancy provided information about an additional 11 patients. Substantiated side effects were nausea or vomiting in seven patients. Anomalies at birth, an undescended testicle and syndactyly, were reported in two children. There was one stillbirth with pathologic findings classic for toxemia, and one fetal death occurred several months after fluorescein angiography. One therapeutic abortion was performed for complications in toxemia. One spontaneous abortion occurred three days after fluorescein angiography in a patient who was four weeks pregnant. Eight children born to toxemic mothers had low birth weights. We conclude that fluorescein angiography does not cause a high rate of birth anomalies or complications during pregnancy.

Occasionally, a vision-threatening lesion occurs during pregnancy. If the lesion requires fluorescein angiography for either diagnosis or treatment, the question of the safety of the procedure arises. Furthermore, women may undergo fluorescein angiography before realizing they are pregnant. Although published reports state that fluorescein angiography should be avoided during pregnancy,[1-7] there is little information about the safety of the procedure during pregnancy.

We surveyed retina specialists to compile information on patients who had fluorescein angiography during pregnancy. All cases in which information about the health of the mother and child were available were included.

Material and Methods

Four hundred twenty-four members of the Retina, Macula, and Vitreous Societies, the Paul Cibis Club, and the Club Jules Gonin were surveyed to identify those who had performed at least one fluorescein angiogram on a pregnant woman in the previous ten years. Specialists who responded affirmatively were contacted for information about each patient.

Follow-up questionnaires requested maternal age, medical history, reason for fluorescein angiography, number of studies performed per patient, and the trimester the study was performed. Side effects were reported, as was any required treatment. The gestational ages of the children were requested. Fetal and neonatal as well as maternal complications were included. The brand and concentration of fluorescein were reported.

Several previous reports described fluorescein angiography during pregnancy.[8-13] If inadequate information was provided in the published case reports, the authors were contacted and asked to complete our questionnaire.

Questionnaires were rejected if they lacked information on fetal, neonatal, or maternal complications.

Results

A total of 424 retina specialists were surveyed and 403 (95%) responded. Three hundred thir-

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teen specialists (78%) said they had not performed even one fluorescein angiography on a pregnant woman during the past ten years. Ninety (22%) had performed at least one.

The 90 specialists were further questioned for information about their patients. Forty-five specialists could not provide additional information because of an inability to identify the patients who had fluorescein angiography during pregnancy. Nine specialists could not be reached for further information.

Thirty-six specialists were able to provide information on 105 patients who had fluorescein angiography during pregnancy in the previous ten years. Forty six of the 105 patients had been described in previous reports[14,15]; further information was obtained as required. An additional six reports added 11 patients, making the total 116.

Nineteen patients underwent fluorescein angiography in the first trimester, 26 patients underwent the procedure in the second trimester, 30 patients underwent the procedure in the third trimester, and 22 patients underwent the procedure in each trimester. Seventy-one patients had one fluorescein angiogram during pregnancy, eight patients had two, 32 patients had three, and two patients had four.

Diabetic retinopathy (40 patients), toxemia of pregnancy (31 patients), and choroidal neovascular membrane (27 patients) were the three most common reasons for fluorescein angiography during pregnancy. Other reasons for the procedure included central serous retinopathy (five patients), vasculitis (two patients), acute multifocal placoid pigment epitheliopathy (one patient), retinal venous occlusion (one patient), optic disk edema (one patient), multiple evanescent white dot syndrome (one patient), sickle cell retinopathy (one patient), choroidal hemangioma (one patient), intracranial hypertension (one patient), and unknown (four patients). Many of the patients with diabetes and toxemia underwent fluorescein angiography as part of a prospective clinical study rather than for diagnostic or therapeutic purposes.

Three of the 116 patients had nausea as a side effect of fluorescein angiography, and four patients had both nausea and vomiting. None of the patients required treatment for these symptoms. There were no patient deaths from fluorescein angiography during pregnancy.

The gestational ages of the children born to the 116 patients were as follows: greater than 34 weeks for 103 children; 28 weeks for one child; and 12 children had unknown gestational ages. Ten diabetic patients required cesarean section. The average maternal age was 27 years.

There were four neonatal or fetal deaths. These are not included in the study for the following reasons: one infant was stillborn, and the placenta had obvious pathologic indications of eclampsia; one therapeutic abortion was performed for complications of eclampsia; one fetal death occurred months after fluorescein angiography (no further information about the presence of fetal anomalies in this child was available); and one spontaneous abortion occurred three days after fluorescein angiography in a four-week pregnancy of an otherwise healthy woman.

Birth anomalies were reported in two children. One child had an undescended testicle, and one child had syndactyly. Eight babies born of patients with hypertension-related pregnancies had a low birth weight.

Fluorescein concentrations ranged from 10% to 25%. There was no correlation of brand, concentration, or timing of fluorescein administration with fetal deaths, fetal anomalies, or patient side effects.

Discussion

Reports about retinal disease during pregnancy have stated that fluorescein angiography was specifically avoided because of possible adverse effects.[1-6] Recent reports, however, stated that no data were available on the use of fluorescein angiography during pregnancy.[7,16]

Reviews about side effects and complications of fluorescein angiography[17-22] do not include complications of fluorescein angiography during pregnancy. Yannuzzi and associates[23] mentioned that pregnancy is a contraindication to fluorescein angiography. Approximately 80% of the 2,434 responding ophthalmologists in their study said they would not perform fluorescein angiography on a pregnant patient. Those who would do the procedure indicated that it should be reserved for vision-threatening lesions and that the study should be performed only in the latter part of pregnancy.

Package inserts for most brands of intravenous fluorescein dye state that injection should be avoided during pregnancy, especially in the first trimester. The inserts also state that no fetal complications have ever been reported from intravenous fluorescein.

The incidence of nausea and vomiting report-

ed in our study was approximately 6% (seven patients). This concurs with the data in other studies.[17-19,23] Furthermore, other side effects such as dizziness, anaphylactoid reaction, rash, and pruritus were not described by any of the patients in this study.

Birth anomalies were rare in this series of 116 patients. Many patients in this study had a higher than normal risk of fetal anomalies (diabetic patients) and fetal mortality (patients with toxemia or sickle cell anemia).[24] Pregnancies complicated by pregnancy-related hypertension have an increased risk of perinatal mortality and growth retardation. Pregnancy-related hypertension accounted for many of the fetal complications described in this study. Diabetic patients have an increased risk of fetal death of approximately 4%, and congenital malformations occur at an increased rate.

Several studies about teratogenicity of fluorescein in animals found no increased incidence of fetal anomalies or deaths when intravenous fluorescein was given in standard doses during early stages of pregnancy.[25-27] One study showed that fluorescein freely crosses the placenta of rats and is found in the fetus for several hours after injection.[26] Fluorescein also crosses the placenta in humans as is shown by the finding of fluorescein dye in amniotic fluid obtained from amniocentesis in a patient 33 weeks pregnant who had undergone fluorescein angiography several days before.[13]

We conclude that fluorescein angiography does not result in a high rate of birth anomalies or complications when performed on a pregnant patient. Based on our data and existing animal data, we believe it is reasonable to perform fluorescein angiography on a pregnant patient when vision is threatened by a choroidal neovascular membrane; fluorescein angiography could affect the patient's treatment or eventual outcome. The decision to perform fluorescein angiography on a pregnant patient is left to the physician and patient, who should carefully weigh the risks and benefits of the procedure. Additionally, we believe that our data can be valuable to ophthalmologists who must advise patients who underwent fluorescein angiography before they knew they were pregnant.

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OPHTHALMIC MINIATURE

"Yow," said Koko. He jumped to the bed and looked at the man with sympathetically blinking eyes. They were sapphire blue in bright light, but in the lamplit hotel room they were large circles of black onyx with flashes of diamond or ruby.

Lilian Jackson Braun, *The Cat Who Turned On and Off*
New York, Berkley Publishing Group, 1986, p. 6

Macroaneurysms Associated With Retinal Branch Vein Occlusion

Scott W. Cousins, M.D., Harry W. Flynn, Jr., M.D., and John G. Clarkson, M.D.

We reviewed the clinical findings, color photographs, and fluorescein angiograms of 147 patients (154 involved eyes) who participated in the Branch Vein Occlusion Study through the Bascom Palmer Eye Institute for the presence of macroaneurysms within or adjacent to the zone of branch vein occlusion. Four distinct categories of macroaneurysms included arterial, venous, capillary, and collateral-associated types. We identified 59 lesions among 25 of the 154 (16.2%) affected eyes. Intraretinal lipid exudation and hemorrhage were commonly observed around the lesions, but these complications usually did not affect visual acuity. Macroaneurysms were associated with capillary nonperfusion on fluorescein angiography. Retinal neovascularization occurred in eight of 25 eyes (32%) with macroaneurysms.

DISTINCTIVE MICROVASCULAR CHANGES develop within the retinal vasculature after retinal vein occlusion. Microaneurysms, telangiectatic and nonperfused capillaries, and dilated collateral vessels are the common sequelae of branch and central vein occlusion.[1] Although the clinical features and course of arterial macroaneurysms have been well established,[2,3] it is not well known that similar macrovascular changes can be associated with retinal vein occlusions.[4] A review of published reports showed five well-documented case reports of these lesions,[5-8] and one additional Japanese series appeared.[9] Nevertheless, it was our clinical impression that macroaneurysms occurred more commonly in venous occlusive disease than these few reports suggested.

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Patients and Methods

We reviewed the clinical, photographic, and angiographic records of 147 patients (154 involved eyes), who enrolled in the Branch Vein Occlusion Study[10,11] through the Bascom Palmer Eye Institute, for the occurrence of macroaneurysms. One of us (J.G.C.) had been the principal investigator for the Branch Vein Occlusion Study and had examined each patient during the follow-up period (1977–1985).

We defined a macroaneurysm on the basis of clinical features, color photographs, and fluorescein angiographic criteria. Clinically, a macroaneurysm was identified from color fundus slides as a red saccular or fusiform structure measuring 100 μm or larger in size. The size was estimated by comparing the macroaneurysm to the diameter of the branch arteries (100 μm) from uninvolved quadrants as they crossed the optic disk. Angiographically, macroaneurysms showed discrete filling of the lesion with dye (Fig. 1) and showed persistent discrete hyperfluorescence for 180 seconds (Fig. 2). The angiographic criteria were based on our impression that microaneurysms and nonaneurysmal structures were not usually hyperfluorescent after 180 seconds, whereas neovascularization usually showed significant leakage by that time.

The size criteria were selected on the basis of the definition by Wise, Dollery, and Henkind,[12] who defined microaneurysms as structures smaller than 100 μm. In this series, macroaneurysms were classified by size: small, 100 to 149 μm; medium, 150 to 249 μm; and large, 250 μm or larger (Table 1).

Four distinct types of macroaneurysms occurred within or adjacent to the zone of branch

Fig. 1 (Cousins, Flynn, and Clarkson). Fluorescein angiogram during the early venous filling phase shows early filling of a large macroaneurysm associated with a collateral vessel (arrow).

Fig. 2 (Cousins, Flynn, and Clarkson). The late phase of the fluorescein angiogram shown in Figure 1 shows persistent filling and dye leakage from the macroaneurysm and the telangiectatic parafoveal capillaries. The macroaneurysm drains into another collateral vessel (arrow) that was not easily identified in the earlier phase of the angiogram.

vein occlusion. Arterial macroaneurysms were identified as saccular or fusiform dilations along major branch arteries or arterioles within the area of branch vein occlusion, with filling from the arterial circulation. Arterial macroaneurysms were indistinguishable from typical idiopathic arterial macroaneurysms except that they were located adjacent to or within the zone of the branch vein occlusion. Venous macroaneurysms were similar-appearing lesions associated with major branch veins or venules, but they exhibited a delay in filling because they filled from the venous circulation. Capillary macroaneurysms were not associated directly with a larger vessel but, on fluorescein angiography, they filled from the adjacent capillary bed and showed no clearly identifiable feeder vessels (Fig. 3). The fourth type of macroaneurysm was the collateral-associated form (Figs. 1, 2, and 4). This last category was associated with clearly identifiable dilated collateral vessels on fluorescein angiography.

TABLE 1
TYPES OF MACROANEURYSMS IN 25 EYES

TYPE	NO. OF LESIONS	LARGE (≥250 μM)	MEDIUM (150–249 μM)	SMALL (100–149 μM)
Arterial	12	2	9	1
Venous	9	2	6	1
Capillary	22	4	12	6
Collateral	16	5	7	4
Total No. of lesions	59	13	34	12

Results

The records of 24 patients (25 eyes) who had macroaneurysms were studied. In these 25 eyes, 59 macroaneurysms were identified.

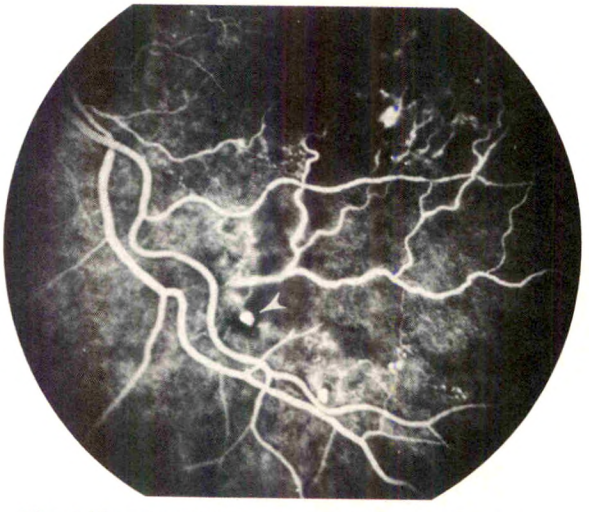

Fig. 3 (Cousins, Flynn, and Clarkson). The fluorescein angiogram shows a medium-sized capillary macroaneurysm (arrow).

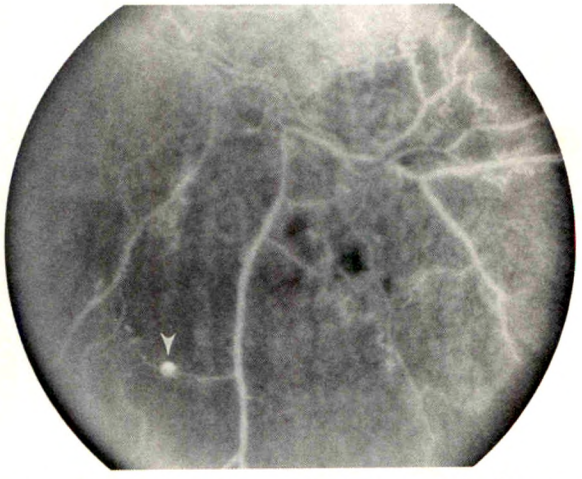

Fig. 4 (Cousins, Flynn, and Clarkson). The fluorescein angiogram shows an isolated collateral-associated macroaneurysm (arrow) in a zone of severe capillary nonperfusion.

Twelve macroaneurysms (20.3%) were small, 34 (57.6%) were medium-sized, and 13 (22.0%) were large. Of the 59 lesions, 12 were arterial, nine were venous, 22 were capillary, and 16 were collateral-associated (Table 1). These lesions, however, were distributed among only 25 of the 154 study eyes (Table 2). Ten eyes had a mixture of aneurysm types, and nearly all possible combinations occurred. Ten eyes had only one lesion, five eyes had two lesions, and ten eyes had three or more lesions.

We also analyzed the course of the macroaneurysms. The mean time of macroaneurysm identification was 23.3 months after entry into the Branch Vein Occlusion Study (range, zero to 72 months). Eleven of 25 eyes (44.0%) had macroaneurysms that involuted within a mean interval of approximately 14.0 months after identification. Additional macroaneurysms developed in 11 of 25 (44.0%) eyes, with an average interval of 40.1 months from the time of detection of the first macroaneurysm to the detection of additional macroaneurysms.

The average age of our patients was 70.6 years. Thirteen (54.2%) patients were women and 11 (45.8%) were men. Of the 25 eyes, 14 received retinal photocoagulation. Six eyes (24.0%) developed clinically significant cystoid macular edema. Fifteen of 24 patients (62.5%) were receiving treatment for hypertension or coronary artery disease. Seven of the 24 patients (29.2%) developed bilateral branch vein occlusions, but only one patient developed bilateral macroaneurysms.

TABLE 2
DISTRIBUTION OF LESIONS IN 25 EYES

TYPE	NO. OF EYES
Arterial	2
Venous	0
Capillary	7
Collateral	6
Mixed types	10
Total No. of eyes	25

The macroaneurysms were associated with a relatively high rate of surrounding intraretinal lipid (ten of 25 eyes [40.0%]) or hemorrhage (nine of 25 eyes [36.0%]). Lipid exudation involving the macula, either associated with the macroaneurysm or with other microvascular changes caused by the branch vein occlusion, occurred in three of 25 eyes (12.0%). Similarly, intraretinal hemorrhage involved the macula only in one eye. In 13 of 25 eyes (52.0%), at least one macroaneurysm was located within the posterior pole. In eyes with multiple lesions, most of the additional macroaneurysms were located peripherally. Most posteriorly located macroaneurysms, however, were far enough away from the macula that lipid exudation or hemorrhage usually did not affect the fovea.

On fluorescein angiography, macroaneurysms were generally associated with capillary nonperfusion adjacent to or near the lesion. Of the 25 eyes with macroaneurysms, 21 (84.0%) were in the "severe nonperfusion" category by the Branch Vein Occlusion Study criteria (at least five disk areas of capillary nonperfusion).[11]

Eight of 25 eyes (32.0%) with macroaneurysms developed neovascularization at some time during the course of the Branch Vein Occlusion Study. However, 14 of the eyes in this study received photocoagulation, which might have altered the course of these eyes by lowering the rate of development of neovascularization. A subgroup of seven eyes had one or more macroaneurysms and a zone of severe nonperfusion in an untreated eye. Within this subgroup, four of seven eyes (57.1%) had or eventually developed neovascularization. An appropriate control group was not available for our study population, which prevented a formal statistical comparison.

Discussion

Macroaneurysms of four distinct types occurred in 25 of 154 (16.2%) eyes studied. Although associated vascular leakage was observed in many of these lesions, most macroaneurysms did not affect vision because most of the lesions were not located in the macula. Such macroaneurysms are easily overlooked clinically because of their noncentral location, the coexistence of other diffuse microvascular changes, and commonly associated diffuse intraretinal hemorrhages.

Although a control group was not available, we compared the characteristics of the eyes we studied to those of the entire Branch Vein Occlusion Study population. The age and sex distribution appeared to be similar. The average age of our patients was 76.0 years. The average age of the patients in the Branch Vein Occlusion Study was not stated, but 90% of the patients were between 50 and 80 years of age.[10,11] Thirteen of 24 (54.2%) of our patients were women, and 146 of the 319 (45.8%) of patients in Group I (three to eight months since onset) of the Branch Vein Occlusion Study and 42 of 82 (51.2%) of those in Group II (similar to Group I, but with retinal neovascularization) were women. Fifteen of 24 patients (62.5%) with macroaneurysms were receiving treatment for hypertension. In the Branch Vein Occlusion Study, 156 of 319 (48.9%) of Group I patients were treated for hypertension, and 15 (5%) were also being treated for diabetes mellitus.

We compared the clinical course of eyes that had macroaneurysms with the course of eyes in the Branch Vein Occlusion Study. Six of 25 eyes (24.0%) developed clinically significant cystoid macular edema in our patient group, and 139 of 502 eyes (27.7%) developed it in the entire study. Seven of the 24 patients (29.2%) developed bilateral vein occlusions in this study as compared to only 9% of patients in the Branch Vein Occlusion Study. In our series, only one patient with bilateral vein occlusions developed a macroaneurysm in each eye. Eight of 25 eyes (32.0%) in our group developed neovascularization. In Group I of the Branch Vein Occlusion Study, 19 of 160 treated eyes (11.9%) and 35 of 159 untreated eyes (22.0%) developed new vessels. However, 27 of 87 untreated eyes (31.0%) with severe (at least five disk areas) capillary nonperfusion eventually developed new vessels. Thus, eyes with macroaneurysms had the same frequency of neovascularization as those with severe nonperfusion in the Branch Vein Occlusion Study.

The clinical significance of a macroaneurysm in an eye with a branch vein occlusion is its association with ischemic retina as demonstrated by capillary nonperfusion on fluorescein angiography. Twenty-one of 25 eyes (84.0%) with macroaneurysms had severe (at least five disk areas) capillary nonperfusion. Eight of the 25 eyes (32.0%) developed neovascularization. In the small subgroup of untreated patients who had severe capillary nonperfusion and a macroaneurysm, however, four of seven (57.1%) of the eyes eventually developed neovascularization.

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Lacrimal Drainage Anomalies in Mandibulofacial Dysostosis

George B. Bartley, M.D.

Seven patients who had the complete form of mandibulofacial dysostosis were examined to determine the prevalence of nasolacrimal abnormalities. Bilateral inferior punctal atresia (and, by implication, accompanying inferior canalicular atresia) was identified in all seven patients; a 95% confidence interval for the true underlying rate of this finding in mandibulofacial dysostosis is 59% to 100%. Lacrimal surgery was required in only one patient who had coexistent bilateral nasolacrimal duct obstruction and chronic dacryocystitis and who responded well to bilateral dacryocystorhinostomy.

MANDIBULOFACIAL DYSOSTOSIS, also known as Treacher Collins syndrome[1] or Franceschetti-Klein-Zwahlen syndrome,[2,3] is a developmental disorder that results in the following characteristic features in affected patients: antimongoloid palpebral fissures, eyelid coloboma, hypoplasia of the maxilla, mandible, and zygomatic process of the temporal bone, malformations of the external and middle ear, macrostomia, and a variety of skeletal and soft tissue deformities (Fig. 1). The eyelid coloboma typically involves the lateral one third of the lower eyelid, and may range from a subtle depression in the eyelid contour to a complete cleft. In the medial two thirds of the lower eyelid, the eyelashes are usually absent or sparse and the eyelid margin is attenuated. Other associated ocular abnormalities such as upper eyelid coloboma, ectropion, entropion, trichiasis, distichiasis, microphthalmos, ectropion pupillae, strabismus, blepharoptosis, refractive errors, and cornea guttata have been noted.[3-5]

Although most studies of mandibulofacial dysostosis have not included details of lacrimal anatomy, absence of the inferior puncta and canaliculi has been noted.[3,5-8] This study was conducted to determine the prevalence of lacrimal drainage anomalies in this disorder.

Fig. 1 (Bartley). Patient 2 at age 2 years with typical features of mandibulofacial dysostosis.

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Patients and Methods

Nine patients with mandibulofacial dysostosis were examined. According to the classification scheme of Franceschetti and Klein,[3] seven patients had the complete form of the disorder, one patient had the incomplete form, and one patient was considered atypical. In addition to clinical examination, nasolacrimal anatomy was studied by dacryocystography in two patients, and the function of the lacrimal drainage system was evaluated by dacryoscintigraphy in two patients. The nasolacrimal system was inspected intraoperatively in one patient who underwent bilateral dacryocystorhinostomy.

Results

None of the seven patients with complete mandibulofacial dysostosis had an inferior punctum in either lower eyelid (Table), and all of the patients had normal-appearing superior puncta (Fig. 2). Only one of the seven patients was asymptomatic (Patient 4). One patient had dry eye symptoms from mild lagophthalmos and used artificial tears. Five of the seven patients had intermittent or constant tearing, and one of the five patients had chronic bilateral dacryocystitis.

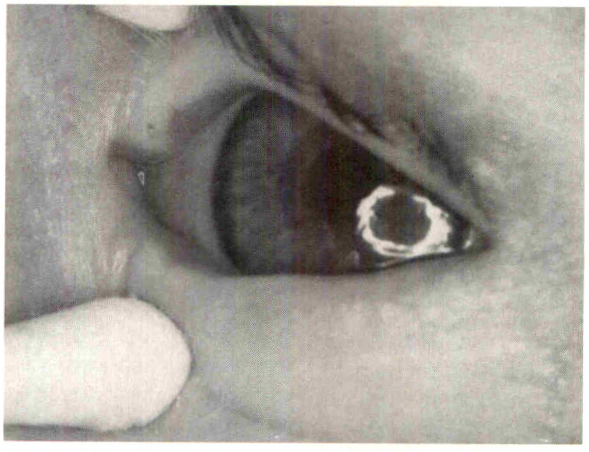

Fig. 2 (Bartley). Patient 3. Absent inferior punctum; superior punctum and canaliculus were normal.

The anatomy of the lacrimal drainage system was evaluated by dacryocystography in two patients. Dacryocystography was performed in Patient 2 while he was under general anesthesia for a craniofacial procedure; the superior canaliculi, lacrimal sacs, and nasolacrimal ducts appeared normal, and there was no evidence of contrast reflux into an inferior canaliculus in either lower eyelid. Patient 3 had chronic bilateral dacryocystitis, and dacryocystography was performed immediately before dacryocystorhinostomy. The superior canaliculi were normal, and there was no apparent contrast reflux into

TABLE
CHARACTERISTICS OF NINE PATIENTS WITH MANDIBULOFACIAL DYSOSTOSIS

PATIENT, AGE (YRS), SEX	CLASSIFICATION*	SYMPTOMS	LACRIMAL FINDINGS
1, 3, F	Complete	Intermittent tearing	Absent inferior puncta
2, 6, M	Complete	Intermittent tearing	Absent inferior puncta; dacryocystography: normal, no reflux into inferior canaliculi
3, 6, M	Complete	Bilateral chronic dacryocystitis	Absent inferior puncta and inferior canaliculi; dacryocystography: normal superior canaliculi, no reflux into inferior canaliculi, dilated lacrimal sacs because of nasolacrimal duct obstruction
4, 9, M	Complete	Asymptomatic	Absent inferior puncta; dacryoscintigraphy: delayed transit bilaterally
5, 12, F	Complete	Intermittent tearing	Absent inferior puncta; dacryoscintigraphy: delayed transit bilaterally
6, 17, M	Complete	Dry eyes	Absent inferior puncta
7, 20, M	Atypical	Asymptomatic	Normal
8, 36, F	Incomplete	Asymptomatic	Normal
9, 41, F	Complete	Intermittent tearing	Absent inferior puncta

*Classification of syndrome according to Franceschetti and Klein.[3]

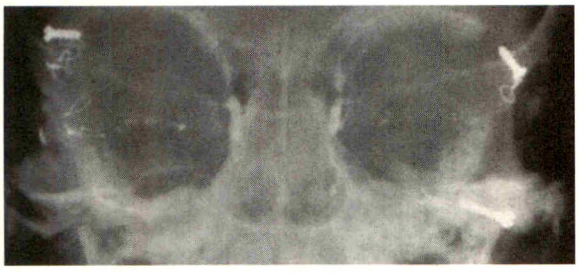

Fig. 3 (Bartley). Patient 3. Dacryocystography demonstrates complete right and subtotal left nasolacrimal duct obstruction. No contrast reflux into inferior canaliculi is apparent.

inferior canaliculi. Each lacrimal sac was moderately enlarged, secondary to complete right nasolacrimal duct obstruction and subtotal left nasolacrimal duct obstruction (Fig. 3). Surgical exploration failed to identify an inferior canaliculus in either lower eyelid.

Dacryoscintigraphy was used to evaluate the function of the lacrimal drainage system in two patients. Although tear flow was delayed in both patients, only one patient (Patient 5) had intermittent tearing. The other patient (Patient 4) was asymptomatic. No nasolacrimal abnormalities were apparent in Patient 7, who had the atypical form of the disorder, and Patient 8, who had the incomplete form and was the mother of Patient 5.

Discussion

Although the common eponym for this syndrome is derived from a report in 1900 of two patients by Co11ins,[1] the disorder had been previously described by Berry[9] in 1888. In 1846, Thomson[10] published his observations on malformations of the ear in several patients who probably had the disorder. In 1944, Franceschetti and Zwahlen[2] proposed the term, "mandibulofacial dysostosis." Five years later, the definitive work on the subject was published by Franceschetti and Klein[3]; the authors reviewed 18 previous cases in published reports, described four additional patients, and outlined five forms of the disorder: complete, incomplete, atypical, abortive, and unilateral. Most patients with mandibulofacial dysostosis have either the complete or incomplete form. The incomplete variant differs from the complete form in that "there is a less striking development of the whole syndrome and the appearance of the ears is almost normal. However, the hearing is often impaired."[3] The atypical and abortive forms are much less common; patients with atypical mandibulofacial dysostosis have eyelid and skeletal abnormalities, whereas the eyelid colobomas are the only reported features apparent in abortive cases. The unilateral form is not accepted by some investigators as a true variant of the syndrome.[11]

Mandibulofacial dysostosis is inherited as an autosomal dominant trait, although most cases result from spontaneous mutations. The pathogenic insult has been hypothesized to occur at the fourth week of gestation and to be related to excessive or premature death of cells derived from the first and second arch ectodermal placodes.[12]

Franceschetti and Klein[3] noted "atresia of the lacrimal canals with purulent conjunctivitis" in one patient with complete mandibulofacial dysostosis and indicated that Waardenburg had described one patient with the incomplete variant who had absent inferior puncta. This feature was subsequently described in three patients who had the complete form of the disorder,[6,8] two patients who had the incomplete form,[5] and one patient who was described as having a combination of the unilateral and atypical forms.[7]

In this study, bilateral inferior punctal atresia was a consistent finding in seven of seven patients with the complete form of mandibulofacial dysostosis. A 95% confidence interval for the true underlying rate of inferior punctal atresia is 59% to 100%. The failure to identify inferior canaliculi by surgical exploration in Patient 3, the lack of contrast reflux into inferior canaliculi during dacryocystography in Patients 2 and 3, and current embryologic concepts of the disorder[11-13] suggest that inferior canalicular atresia is concomitant with inferior punctal atresia in the complete form of mandibulofacial dysostosis. An observation by O'Connor and Conway[6] that the superior puncta are "exceptionally large," thus facilitating tear drainage and precluding epiphora, was not corroborated by this study. No lacrimal abnormalities were identified in one patient who had the incomplete form and one patient who had the atypical form of the syndrome.

Only one patient (Patient 3, who had bilateral dacryocystitis) in this study required lacrimal surgical intervention, although intermittent tearing was a symptom in four of the seven patients who had complete mandibulofacial dysostosis. One patient was asymptomatic, and

one patient had dry eyes. The characteristic downward sloping of the palpebral fissures may create both a problem (mild ocular exposure) and a remedy (a delay in tear flow to the superior canaliculus, thus enhancing ocular lubrication). If keratoconjunctivitis sicca worsens with increasing age, it is possible that the absent inferior puncta actually may be beneficial if it is considered as a physiologic punctal occlusion. Indirect evidence supports this concept; of seven additional adult patients with mandibulofacial dysostosis interviewed by telephone but not examined in this study, six patients were asymptomatic and one patient had dry eyes. It seems reasonable, therefore, to recommend that inferior punctal atresia with only mild intermittent tearing in young patients with mandibulofacial dysostosis be treated conservatively.

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Laser and Unsutured Sclerotomy in Nanophthalmos

Jia Chi Jin, M.D., and Douglas R. Anderson, M.D.

Among 30 eyes with nanophthalmos, 21 had angle-closure glaucoma and two had open-angle glaucoma associated with pseudoexfoliation of the lens capsule. Laser iridotomies, sometimes combined with laser iridoplasty, were sufficient to control, or to allow medical control of, the glaucoma in 15 of 18 eyes. Four eyes with uveal effusion underwent an unsutured sclerotomy or sclerectomy, and all had resolution of the choroidal detachment within two weeks. Cataract extraction improved the vision in seven of nine eyes. Previous or simultaneous sclerotomy or sclerectomy was performed on all nine eyes that underwent cataract extraction and in two eyes at the time of glaucoma surgery; no eye had postoperative uveal effusion or other major complications. Laser iridotomy and iridoplasty, sometimes with supplemental medical therapy, are often sufficient in the treatment of angle-closure glaucoma in nanophthalmos and are safer than surgery. Nanophthalmic uveal effusion can be prevented or treated with an unsutured sclerotomy or sclerectomy.

NANOPHTHALMOS is a rare disease in which the eye is small with intraocular crowding and a thick sclera.[1-6] The lens is of normal volume but is disproportionately large compared to the size of the eye,[2,5] and there are no other ocular or associated systemic developmental abnormalities. Severe hyperopia and angle-closure glaucoma are typical. Uveal effusion may occur spontaneously,[5,7,8] but massive uveal effusion, retinal detachment, intraocular hemorrhage, and malignant glaucoma are especially apt to occur after surgery for cataracts or glaucoma.[3,6,9,10] In recent years, we have often been able to control the glaucoma noninvasively by laser therapy. We have also found that unsutured sclerotomies or sclerectomies have cured uveal effusion, or have prevented uveal effusion and its sequelae when used prophylactically at the time of anterior segment surgery for glaucoma or cataracts.

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Material and Methods

We retrieved the medical records of all patients with the diagnosis of microphthalmia or nanophthalmos seen by any physician at the Bascom Palmer Eye Institute between January 1982 and July 1989. Among 162 records, 30 eyes of 15 patients were identified as having nanophthalmos based on their characteristic anatomic features and clinical courses, as well as echographic results. Nanophthalmos was distinguished from other types of microphthalmia (typically associated with other ocular or systemic development defects)[1] and from uveal effusion not associated with small ocular dimensions.[11-14] Features we considered characteristic of nanophthalmos were a small eye with a small cornea, a shallow anterior chamber, moderate-to-severe hyperopia, a short axial length, and diffuse choroidal-scleral thickening as disclosed by echography. A tendency to develop angle-closure glaucoma and uveal effusion were also considered typical.

For each patient, the following information was tabulated for analysis: sex; ages at initial examination and at the onset of glaucoma; family history of glaucoma, nanophthalmos, or blindness; visual acuity and refractive error; intraocular pressure; gonioscopic findings; ophthalmoscopic observations; echographic findings; indications for any laser and surgical therapy performed; and short-term or long-term complications of treatment, including uveal effusion, a flat anterior chamber, exudative retinal detachment, intraocular hemorrhage, and malignant glaucoma.

In this study, the term iridoplasty refers to

shrinkage of peripheral iris stroma by heating the iris with laser,[5,15] a procedure which is also called gonioplasty. The term sclerectomy refers to the removal of a two-thirds thickness rectangle of sclera about 5 × 7 mm, usually with removal of a 1-mm full-thickness piece in the bed.[13,14] The term unsutured sclerotomy means that a V-shaped incision was made through the full thickness of the sclera into the suprachoroidal space. The purpose of both sclerectomy and unsutured sclerotomy is to leave an open drainage channel from the choroid. These procedures differ from a drainage procedure in which a slit is made through the sclera and is sutured shut after the suprachoroidal space has been emptied.

The outcome of treatment was judged in terms of visual function, intraocular pressure, complications of therapy, and any need for additional surgery.

Results

Of the 15 patients, 13 (87%) were women. The age range of patients at the first visit was 5 to 80 years with an average of 47.1 years and a median of 51 years. Age at the most recent follow-up examination averaged 55.9 years. All 30 eyes were hypermetropic (Table). Although the hyperopia could be as little as +2.75 diopters, 27 eyes (90%) had more than +5.00 diopters of hyperopia. In 11 eyes (37%), the refractive correction was between +10.00 and +16.50 diopters. By echography of 28 eyes of 14 patients, the average axial length was 18.78 mm (range, 15.7 to 20.5 mm), and 24 of the 28 eyes (86%) showed diffuse chorioscleral thickening.

Among the 30 eyes, 23 eyes (77%) of 12 patients (80%) had glaucoma, including acute angle-closure (nine eyes), chronic angle-closure (12 eyes), and open-angle glaucoma with pseudoexfoliation of the lens capsule (two eyes). A family history of glaucoma or blindness was reported in eight (67%) of the 12 patients in whom a family history was obtained. Diffuse choroidal thickening occurred in 12 (86%) of 14 patients in whom echography was obtained (24 eyes [86%]).

Of the 21 eyes with angle-closure glaucoma, 18 eyes were treated with laser iridectomy as the initial procedure, with simultaneous iridoplasty in three eyes. In all eyes, the iridotomy remained open during the follow-up of one to seven years. Laser iridoplasty was performed on three additional eyes one to two years later. Of the 18 eyes, all but three had satisfactory vision and medically controllable intraocular pressure after having only laser therapy. One patient later had a successful result (intraocular pressure of 10 mm Hg and visual acuity of 20/70 after removal of a cataract present before first visit that had reduced visual acuity to 8/200) after filtering surgery with 5-fluorouracil[16] combined with cataract extraction and a posterior sclerotomy. For another eye, laser iridoplasty has been recommended for late recurrence of increased intraocular pressure, but the procedure has not yet been performed. The third eye whose condition was not controlled by initial laser treatment had a loss of visual acuity to hand motions because of glaucomatous nerve damage, corneal decompensation, and severe macular pucker. This eye, although originally controlled by laser therapy, later underwent cataract extraction, penetrating corneal transplant (three times), vitrectomy (two times), and filtering surgery (two times).

The other three eyes of the 21 with angle-closure glaucoma did not have laser treatment but underwent surgical peripheral iridectomy, which was combined with sclerectomy in two patients. In all three eyes, surgery was successful in controlling the glaucoma, but in the eye that did not undergo prophylactic sclerectomy, uveal effusion occurred after six years. The

TABLE
CHARACTERISTICS OF NANOPHTHALMOS

CHARACTERISTIC	NO. OF EYES (PATIENTS)	AVERAGE	MEDIAN	RANGE	
				MINIMUM	MAXIMUM
Refractive error (D)	30 (15)	+9.48	+8.25	+2.75	+16.50
Age at diagnosis of glaucoma (yrs)	— (12)	48.2	52.5	8	80
Axial length (mm)	28 (14)	18.78	19.2	15.7	20.5
Lens thickness (mm)	14 (7)	4.92	4.65	4.2	6.0

pressure in this eye persists at 30 mm Hg, and filtering surgery is presently under consideration.

Two eyes (one patient) with glaucoma had open angles with pseudoexfoliation of the lens capsule. One eye required surgery in 1984 in the form of a 5-fluorouracil filtering procedure performed after unsuccessful laser trabeculoplasty.[17,18] The 5-fluorouracil filtering procedure (not combined with posterior sclerotomy) was complicated postoperatively by massive uveal effusion and exudative retinal detachment, which, however, resolved after a posterior sclerotomy. Four years later, the filtration bleb gradually collapsed, and the intraocular pressure rose above 30 mm Hg despite full medical therapy. The visual acuity dropped to hand motions because of glaucomatous nerve damage and cataract. The other eye of this patient had been treated with medication solely for seven years, but the most recent examination disclosed a 0.6 cup/disc ratio, which had been 0.2 when the medical therapy was started. The visual field showed a progressive depression, and laser trabeculoplasty has been recommended for this eye.

Of the 23 eyes with glaucoma, the conditions of five eyes are presently uncontrolled. Laser therapy is currently being considered for two of these eyes and filtering surgery for one. The other two eyes have undergone many surgical procedures but have permanent vision loss, so no further treatment is being considered for their uncontrolled glaucoma.

Cataract extraction was performed on nine eyes of five patients. All eyes except one had previous laser or surgical treatment for their glaucoma or uveal effusion. A posterior sclerotomy was performed simultaneously with extracapsular cataract extraction in seven eyes, and in two eyes it had been performed one and seven years before extracapsular cataract extraction. In one eye, the extracapsular cataract extraction was combined with penetrating keratoplasty and vitrectomy and posterior sclerectomy. In another eye, the extracapsular cataract extraction and posterior chamber lens implantation was combined with a 5-fluorouracil filtering procedure and posterior sclerotomy. None of the nine eyes had postoperative uveal effusion, retinal detachment, intraocular hemorrhage, or malignant glaucoma. In seven of the nine eyes, the visual acuity improved (to 20/400 in three eyes and to 20/60 or better in the other four eyes). Of the two eyes with only hand motions visual acuity, one was the eye that had undergone many operations. Its vision was impeded by corneal edema and uncontrolled glaucoma. The other eye with hand motions visual acuity had a macular scar from a retinal detachment that existed before the extracapsular cataract extraction. All but one eye maintained glaucoma control within the follow-up period of one to 72 months.

Five eyes of three patients (ages 11, 47, and 68 years) did not require laser treatment or surgery for cataract or glaucoma during an observation period of four to six years. These eyes had neither glaucoma nor uveal effusion. One of these patients was 5 years old when she was first seen. During the six years of follow-up, there was no noticeable narrowing of the anterior chamber angle. Her visual acuity improved from 20/60 to 20/30 with correction of the hyperopia.

Choroidal detachment occurred in seven eyes of five patients, four of whom were women. In two eyes, the choroidal detachment was associated with nonrhegmatogenous retinal detachment. The choroidal effusion occurred spontaneously in two eyes of two patients and occurred after laser iridectomy in three eyes. In one eye, it occurred six years after a surgical iridectomy, and in one eye a massive uveal effusion occurred immediately after a 5-fluorouracil filtering operation (without posterior sclerotomy).

Of the seven eyes with choroidal effusion, three were treated without sclerotomy. One eye had a small choroidal detachment that had been waxing and waning in the inferior part of the fundus over the six years of follow-up, and the vision was becoming worse because of cataract. The other two eyes are of a patient who had been observed to have "total choroidal fold" in both eyes for four years, beginning one year after laser iridotomies. In these two eyes, the ultrasonic diagnosis of uveal effusion was made after the eyes had suffered severe loss of vision caused by cystic maculopathy in both eyes.

A posterior sclerotomy was performed in the other four eyes. Two eyes had highly elevated choroidal and exudate retinal detachment. In all four eyes, the choroid was reattached within two weeks, and the exudative retinal detachment resolved within eight weeks after the procedure. In no eye did uveal effusion recur during the follow-up period of 36 to 72 months. In one eye, the posterior sclerotomy was combined with a scleral buckling procedure for the 360-degree highly elevated uveal effusion and

retinal detachment. In another eye, the successful unsutured sclerotomy was performed to relieve large, centrally apposed choroidal detachments and overlying retinal detachment with hand motions visual acuity. In this eye, the choroidal detachment had been present for a year, having recurred immediately after a drainage through a sclerotomy that was sutured closed. After the unsutured sclerotomy, the uvea and retina were reattached completely, and the visual acuity returned to 20/40. In six years there has been no recurrence.

Eleven eyes underwent sclerectomy or unsutured sclerotomy prophylactically at the time of glaucoma surgery or cataract extraction, and none had postoperative uveal effusion.

Discussion

Disastrous results of surgical intervention in nanophthalmos have been documented in several reports.[2,3,6,9,10] In the largest reported series, Singh and associates[6] described the results of treatment of 32 eyes. Of 15 eyes on which glaucoma surgery was performed, 13 (86%) had loss of vision after surgery. Only three of six eyes (50%) had visual improvement after cataract surgery. Despite such a discouraging prognosis, surgery has often become unavoidable because of medically uncontrolled glaucoma or advanced cataract, and alternate methods are tried. Our experience suggests that there has been a better outcome in recent years with the use of laser iridotomy and iridoplasty and the use of unsutured sclerotomies or sclerectomies.

Laser therapy has succeeded in controlling the glaucoma in most patients. Some patients have required iridoplasty[5,15] to widen angles that remain crowded after iridotomy. Although uveal effusion can occur after laser therapy, or indeed spontaneously, it may be less frequent than after surgical iridectomy. Should uveal effusion occur, spontaneously or after laser treatment, prompt recognition and the use of an unsutured sclerotomy should lead to a satisfactory outcome. Reports of uveal effusion and other complications from invasive surgery do not constitute a reason to delay laser iridotomy and iridoplasty as needed. Early laser therapy (that is, before extensive goniosynechiae develop) is important if filtration surgery is to be avoided.

A sclerectomy or unsutured sclerotomy was performed to treat uveal effusion and was also combined routinely with glaucoma and cataract surgery to prevent uveal effusion and other complications, such as intraocular hemorrhage, malignant glaucoma, and a flat anterior chamber. In the four eyes that underwent a therapeutic sclerectomy or sclerotomy, the choroidal effusion resolved within two weeks. Similar success was reported in two other patients.[10,19] Uveal effusion occurred in the two eyes that underwent glaucoma surgery without prophylactic posterior sclerotomy, and this is expected in cases of nanophthalmos.[6,9,10] In our series, uveal effusion was avoided in all nine eyes that underwent cataract extraction and prophylactic sclerectomy or unsutured sclerotomy and in both cases of surgical iridectomy combined with sclerectomy.

In our earlier operations, the sclerectomy technique involved removing a partial (2/3) thickness patch of sclera 5 × 7 mm in several quadrants with a full-thickness sclerectomy 1.5 mm in diameter in the bed of each patch.[13,14] In more recent operations, we used a V-shaped full-thickness sclerotomy over the pars plana and left it unsutured to provide ongoing drainage postoperatively. We now believe the drainage site is best made anteriorly, over the pars plana. A posterior scleral weakness is at risk of rupture with vitreous and retina incarceration, whereas the anterior site is better protected by a thicker uveal layer and a firm vitreous base. Additionally, Calhoun[9] had reported that three cases of nanophthalmos glaucoma treated with peripheral iridectomy or lens extraction combined with a sclerectomy made posteriorly had resulted in vitreous hemorrhage, exudative retinal detachment, and vitreous bands, and all of the eyes lost vision. We also believe that sclera need not be removed, but that it is sufficient to make a V-shaped drainage incision and leave it open to provide a persisting route for escape of proteinaceous suprachoroidal fluid. In one eye, choroidal effusion and retinal detachment of sufficient magnitude to be centrally apposed recurred after drainage through a sclerotomy that was sutured closed, but did not recur for six years after a subsequent unsutured sclerectomy.

The rationale for use of unsutured sclerotomy or sclerectomy is based on the hypothesis that uveal effusion results from reduced transscleral exit of choroidal fluid.[14,20] The extracellular fluid of the choroid normally contains protein that physiologically escapes from the blood vessels.

Because the protein cannot be reabsorbed by uveal blood vessels, it exits in solution by transscleral outflow,[21] driven by the intraocular pressure. Such outflow may be impeded by the reduced surface area of a small globe, a thickened sclera, a reduced number of transscleral channels (such as around vortex veins), or an altered character of the scleral extracellular material.[22,23] These features of nanophthalmos may produce a tendency for accumulation of choroidal fluid.[5,8] The accumulation may occur spontaneously but is aggravated by excessive protein leakage from vessels during inflammation and reduced transscleral hydrostatic pressure during hypotony. These aggravating pathogenic elements may account for uveal effusion after surgery.[2,3,6,9,10] The pathophysiologic mechanism in nanophthalmos perhaps shares features with that of spontaneous uveal effusion or postoperative choroidal detachments that occur in eyes without nanophthalmos.[11-14,24-26] The effectiveness of an unsutured sclerotomy in curing or preventing uveal effusion supports the concept that inadequate transscleral outflow contributes to the production of uveal effusion. The benefit of dissection around vortex veins[8] may not result from decompressing the venous drainage, but from opening channels for transscleral drainage.[13,14,27] Transscleral channels made remote from vortex veins seem just as effective with less risk of hemorrhage.

Based on this understanding of the pathophysiologic mechanism and on the results in the present series, we recommend that an unsutured anterior V-shaped sclerotomy be performed whenever intraocular surgery is performed in a nanophthalmic eye to avoid the severe postoperative complications typical of nanophthalmos.[3,10] To use prophylactic sclerotomy appropriately, it is important to recognize the eyes at risk of postoperative uveal effusion, namely severely hyperopic eyes with small corneas and crowded anterior segments. Other diagnostic clues for nanophthalmos include a pupil that dilates poorly, a wide-pulse amplitude of the intraocular pressure, a narrow palpebral fissure, and regions of spontaneous choroidal detachment.[4-9] When nanophthalmos is suspected, echography may document a short axial length or a thick chorioscleral wall.

We also recommend that an unsutured sclerotomy be performed to treat uveal effusion that has already occurred spontaneously or postoperatively, provided that the effusion is of sufficient magnitude to contribute to angle crowding anteriorly or visual disturbance posteriorly.

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OPHTHALMIC MINIATURE

The glimpses of external reality presented in this book must therefore be seen as the interaction between two moving objects: the scene observed and the pair of eyes that observed it . . . . For one of the keys to the understanding of the human predicament is the recognition that there is, for the human individual, no reality—no comprehensible and useful reality, at any rate—other than that of an object as perceived by the human eye and the human mind—no abstract reality, in other words, detached from the eye of the beholder. All that we see around us may be considered to some extent as a part of ourselves, the reflection of our own astigmatisms, our own individual perspectives, and—sometimes—our intuitions. Unless it is taken that way, we cannot recognize its reality, or even know it to be real.

G. F. Kennan, *Sketches From a Life*
New York, Pantheon Books, 1989, p. xiii

Scalpel Neodymium:YAG Laser in Oculoplastic Surgery

Allen M. Putterman, M.D.

In a three-year study, the scalpel Nd:YAG laser was compared with conventional surgery in 18 patients who underwent oculoplastic surgery. The postoperative follow-up was at least eight months. The contact Nd:YAG laser had distinct advantages over conventional surgery in the treatment of vascular orbital tumors, including less perioperative bleeding and a shorter operating time. In other oculoplastic procedures, ten of the 18 patients underwent surgery with the scalpel Nd:YAG laser on one side and conventional surgery on the other side. There was less bleeding, a shorter operating time, and less pain on removal of orbital fat on the laser-treated side. The postoperative scarring was initially more noticeable on the Nd:YAG laser-treated side, but after three months there was no appreciable difference in scar formation between the two sides. The amount of postoperative edema and ecchymosis did not appear to be significantly different with the Nd:YAG laser compared with conventional surgery. Additionally, microscopic evaluation showed minimal charring of tissues with the Nd:YAG laser.

Laser power with the Nd:YAG laser can be transmitted through a fiberoptic coil to a probe with a sapphire tip. The tip, when touched to tissue, creates an incision while simultaneously coagulating bleeding sites. This laser differs from noncontact lasers, which rely on the transmission of laser energy through air to a specific location.

To investigate whether the scalpel (contact) Nd:YAG laser has advantages over conventional techniques in oculoplastic surgery, I conducted a three-year experimental study (postoperative follow-up, ≥8 months). Eighteen patients underwent oculoplastic surgical procedures with the use of the sapphire-tip Nd:YAG laser, ten of whom received laser treatment on one side and conventional surgery with a surgical blade and scissors on the other side.

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Patients and Methods

Oculoplastic surgery was performed with the scalpel Nd:YAG laser in 18 patients (Table). In four of these patients, an experimental portable Nd:YAG laser was attached to fiberoptic coils and sapphire tips. In nine patients, fiberoptic coils and sapphire tips were attached to a stationary Nd:YAG laser. In the remaining five patients, a commercially available portable Nd:YAG laser unit was attached to the manufacturer's fiberoptic coils and sapphire tips. The first (experimental) laser had a power source that ranged from 0 to 10 W, whereas the other two machines ranged from 0 to 60 W in power. For the procedures performed in this study, a power setting of 6 to 16 W was used. For blepharoplasties, an 8-W setting was usually used for the skin incision, and 10 to 12 W of power was used for severing subcutaneous tissues.

The sapphire tips used were clear or frosted and varied in size. The clear tips were used for skin because they produce a finer incision and less charring of tissue than do the frosted tips. The frosted tips were used for dissection of subcutaneous vascular tissue because these tips coagulate bleeding sites better than do the clear tips. Usually a 4-mm tip was used because the smaller tips produce a thinner incision. Protective glasses of an optical density of at least 4.5 at a 1,064-nm wavelength were used by the operating staff, while the patient's eyes were protected with large green scleral lenses that are used in routine oculoplastic procedures.

Five patients with dermatochalasis and her-

TABLE
YAG LASER OCULOPLASTIC SURGICAL PROCEDURES

NO. OF PATIENTS	PROCEDURE	SITE	
		YAG LASER	CONVENTIONAL SURGICAL TECHNIQUES
5	Excision of skin, orbicularis muscle, and orbital fat	Left upper and lower eyelids	Right upper and lower eyelids
1	Excision of skin, orbicularis muscle, and orbital fat	All four eyelids	Not done
3	Excision of skin, orbicularis muscle, and orbital fat with levator muscle aponeurosis resection	Left upper eyelid	Right upper eyelid
1	Excision of skin, orbicularis muscle, and orbital fat with levator muscle aponeurosis resection	Right upper eyelid	Not done
1	Excision of skin, orbicularis muscle, and orbital fat with capsulopalpebral fascia advancement entropion procedure	Left lower eyelid	Right lower eyelid
1	Direct brow lift	Left upper eyelid	Right upper eyelid
1	Coronal brow lift	Both brows	Not done
2	Vascular orbital tumor	Left orbit	Not done
1	Vascular orbital tumor	Right orbit	Not done
1	Retrobulbar malignant orbital tumor	Left orbit	Not done
1	Dacryocystorhinostomy	Right eye	Not done

niated orbital fat of all four eyelids had upper and lower eyelid surgery performed on one side with the scalpel Nd:YAG laser and on the other side with conventional techniques using a No. 15 Bard-Parker blade, Westcott scissors, and disposable and Bovie surgical cauteries. In an additional patient, the laser was used on both sides. The procedures in the upper eyelids involved excision of skin, orbicularis muscle, and orbital fat with suturing of the levator muscle aponeurosis to orbicularis muscle to form an eyelid crease (Fig. 1).[1] In the lower eyelids, a skin-muscle flap was created to identify the herniated orbital fat, which was then removed from all three lower fat pockets.[1]

Four additional patients had acquired blepharoptosis that was treated by a levator muscle aponeurosis resection.[2] The technique was similar to that used for upper blepharoplasty with incision of skin and orbicularis muscle and resection of orbital fat. Additionally, the resected levator muscle aponeurosis was sutured to tarsus and skin. In three of the patients, the blepharoptosis was bilateral, and the Nd:YAG laser was used on one side and conventional surgery was performed on the other side. The other case of blepharoptosis was unilateral, and the Nd:YAG laser was used alone.

One patient had bilateral acquired lower eyelid entropions. The capsulopalpebral fascia was identified after an incision through skin and orbicularis muscle. Orbital fat was resected, and the capsulopalpebral fascia was attached to the inferior tarsal border and skin.[3] The eyelid was also horizontally shortened through a lateral canthotomy, cantholysis, and tarsal strip procedure.[1] On one side, the Nd:YAG laser was used. On the other side, conventional surgery was performed using a No. 15 Bard-Parker blade for the incision of skin, and Westcott scissors were used for severing the orbicularis muscle and lateral canthus; orbital fat was resected in the same manner as that for the blepharoplasty and blepharoptosis procedures.

In another patient, a direct brow lift was performed on one side with the Nd:YAG laser and on the other side by conventional techniques with a No. 15 Bard-Parker blade and Westcott scissors. On each side, an ellipse of skin and frontalis muscle was removed, which measured approximately 10 mm vertically and 50 mm horizontally.[1] An additional patient had a coronal brow lift, and the laser was used to make the hairline incision from skin to periosteum on each side.[1]

In the above patients, a No. 2 or 4-mm clear sapphire tip was used to make the skin incisions with the laser, and the 4-mm frosted tip was used to cut through orbicularis muscle and to remove orbital fat.

Tumors of the eyelid and orbit were removed in four patients. Three tumors were vascular. The Nd:YAG laser was used to make an incision through the skin and to cut skin and orbicularis

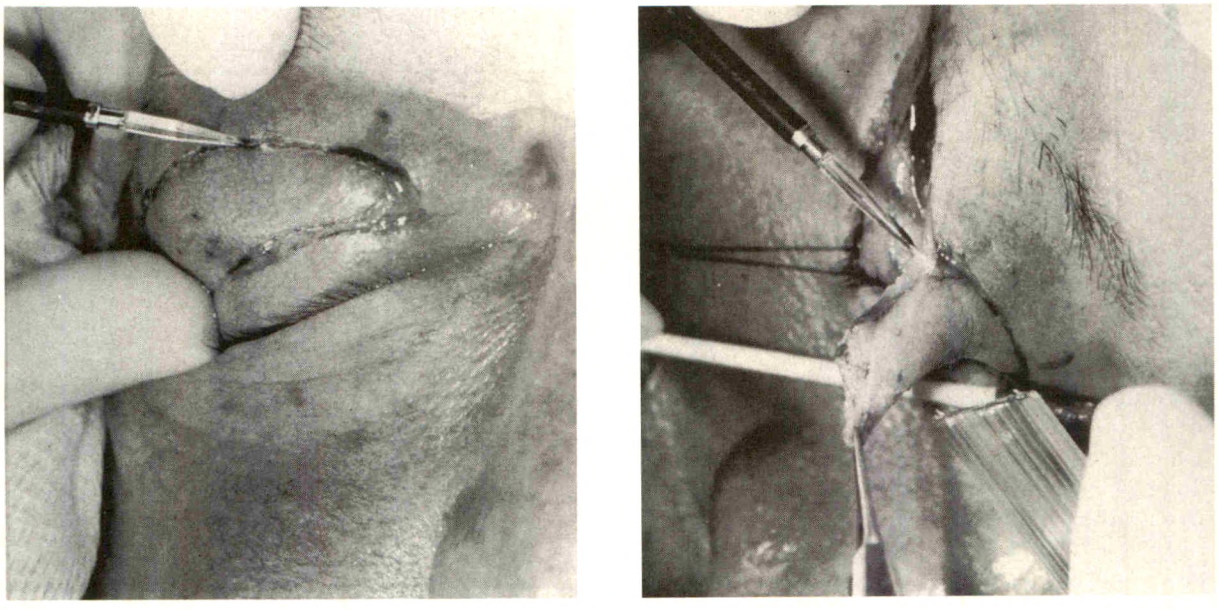

Fig. 1 (Putterman). Left, Scalpel Nd:YAG laser used during cosmetic blepharoplasty of the upper eyelids to incise skin. Right, Scalpel Nd:YAG laser used to sever orbicularis muscle during resection of ellipse of skin and orbicularis muscle.

muscle from the tumors (Fig. 2). In these patients, the clear 4-mm tip was used to make the incision through skin and orbicularis muscle, and the frosted 4-mm tip was used to cut orbicularis muscle from the tumor, and in lateral orbitotomies it was used to cut through orbicularis muscle and periosteum.

One dacryocystorhinostomy was attempted with the Nd:YAG laser. The incision through skin, orbicularis muscle, and periosteum was made with the laser. Even though the power was increased to 30 to 40 W, it was not possible to penetrate bone.

Results

In this series of patients, less bleeding occurred on the side on which the scalpel Nd:YAG laser was used than on the side that underwent conventional surgery. The surgery performed on the laser-treated side was, therefore, faster because less time was spent controlling bleeding with the surgical cauteries. Up to 20 minutes was saved with the Nd:YAG laser.

The patients reported less pain on the removal of orbital fat with the Nd:YAG laser than with conventional surgery. With the laser, the fat was removed by lifting it up with forceps and rubbing the laser tip over the base of the prolapsed fat. This approach differs from the conventional technique of fat resection, which involves clamping the prolapsed fat with a hemostat, cutting it with a No. 15 Bard-Parker blade slid over the hemostat, placing cotton-tipped applicators under the hemostat, and applying a Bovie cautery to the hemostat.[1]

Photographs of the patients were taken one,

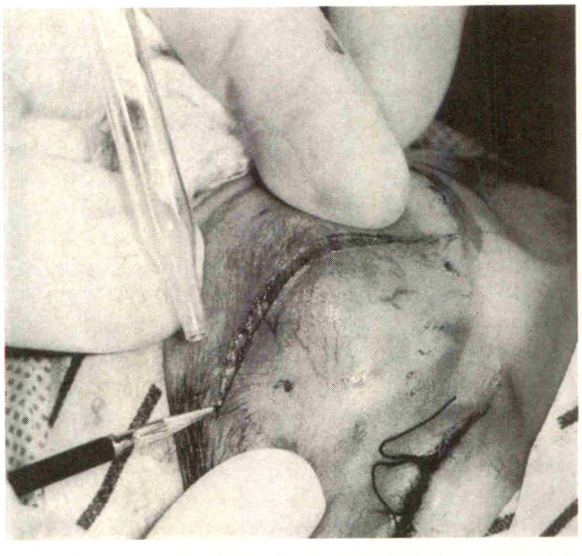

Fig. 2 (Putterman). Scalpel Nd:YAG laser used to make skin incision and dissect skin from a vascular orbital tumor.

three, six, and 12 weeks postoperatively. An unbiased physician observer compared these photographs and noted no significant difference in ecchymosis or edema between the Nd:YAG laser–treated side and the conventionally operated on side. The observer noted that the scars on the side that underwent the Nd:YAG laser procedures were more noticeable during the first few weeks postoperatively compared with the side that underwent conventional surgery. At 12 weeks postoperatively, however, there was no noticeable difference between the two sides.

In the four patients with eyelid and orbital tumors, bleeding was minimal and greatly reduced with the use of the scalpel Nd:YAG laser, whereas removal of these types of tumors in other patients with conventional surgical procedures was complicated by severe bleeding. For example, before the first orbital arteriovenous malformation tumor treated with the Nd:YAG laser, a similar case had been treated with conventional techniques. The conventional surgery was performed by making a skin-orbicularis muscle incision at the crease of the upper eyelid and dissecting the tumor with Westcott scissors. There was severe hemorrhaging, and it took three hours to remove the tumor and control the bleeding. The Nd:YAG laser procedure in another patient lasted 15 minutes. With several sweeps of the Nd:YAG laser, the incision through skin and orbicularis muscle was made, and the laser tip was brushed along the tumor until it was vaporized. Subsequently, the skin incision was sutured with a continuous suture. Another orbital tumor was a retrobulbar malignant neoplasm, which was treated with the Nd:YAG laser to make a Wright incision through skin, orbicularis muscle, and periosteum over the superior and lateral orbital rims and zygomatic arch.[4] There was less bleeding than in many other patients in whom a similar incision was created with a No. 15 Bard-Parker blade.

Pathologic specimens obtained during Nd:YAG laser treatment and surgical blade-scissors treatment of the three patients with blepharoplasty, the one patient with brow ptosis, and the one patient with blepharoptosis were studied. It was found that the Nd:YAG laser caused minimal charring of tissue compared with what occurs with the Bovie cauteries or other coagulative techniques. There was, however, more charring than occurs with conventional surgery using a surgical blade.

Discussion

The scalpel Nd:YAG laser has been shown to be useful in plastic surgical procedures.[5,6] More experimentation using the contact Nd:YAG laser in oculoplastic surgery is needed to define its usefulness better. Presently, the laser has distinct advantages over conventional surgery in the removal of vascular tumors because it leads to less bleeding. In other oculoplastic surgical procedures, such as blepharoplasty or correction of blepharoptosis, entropion, and brow ptosis, there is an obvious decrease in bleeding and operating time when the Nd:YAG laser is used compared with conventional surgery performed with a surgical blade and Westcott scissors. An additional advantage of the Nd:YAG laser is less pain on resection of orbital fat, probably because the herniated orbital fat does not have to be pulled as much as it does in conventional surgery. The early scarring of the skin when the Nd:YAG laser is used is more apparent than with conventional surgery, but after three months there does not seem to be any appreciable difference. Additionally, there does not seem to be any appreciable difference in the amount of swelling and ecchymosis with the Nd:YAG laser compared with conventional surgery. Pathologic specimens show minimal charring of tissue with the scalpel Nd:YAG laser.

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Cobalt-60 Plaque Radiotherapy vs Enucleation for Posterior Uveal Melanoma

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We compared the survival of 302 patients with a primary choroidal or ciliary body melanoma treated by cobalt-60 plaque radiotherapy between 1976 and 1982 with the survival of 134 patients treated by enucleation during the same period. Tumor size, location of the anterior margin of the tumor, and patient age at the time of treatment were identified as simultaneous significant clinical variables for predicting melanoma-specific mortality by multivariate Cox proportional hazards modeling. We computed a prognostic index for each patient based on this model and found that patients in the enucleation group had slightly higher values of this index than did patients in the cobalt-60 plaque radiotherapy group. Risk ratios for the treatment effect computed from a Cox model incorporating prognostic index and the treatment variable were found to be approximately equal to 1, both for analysis of melanoma-specific mortality and total mortality. These results indicate that when one controls for differences in prognostic index between the groups, cobalt-60 plaque therapy and enucleation are essentially equivalent in their effect on survival.

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DESPITE PUBLISHED REPORTS that indicate essentially equivalent melanoma-specific mortality rates in statistically matched groups of patients with primary choroidal or ciliary body malignant melanoma treated by enucleation vs episcleral plaque radiotherapy[1-3] or charged-particle irradiation,[4] there is currently no consensus about the relative effectiveness of these treatments. In an attempt to clarify this issue, a multicenter, randomized clinical trial of enucleation vs plaque radiotherapy for intermediate-risk patients with choroidal malignant melanoma was recently initiated.[5] The results of that trial, however, will not be available for at least several years. At Wills Eye Hospital, a nonrandomized clinical study of enucleation vs episcleral plaque radiotherapy in patients with primary posterior uveal melanoma has been in progress since 1976. Preliminary results of this study have been published.[1]

Subjects and Methods

A total of 601 patients with a primary choroidal or ciliary body malignant melanoma were treated initially by either enucleation (247 patients) or cobalt-60 plaque radiotherapy (354 patients) at Wills Eye Hospital between May 1976 and December 1982. The methods of clinical examination, diagnosis, treatment, and follow-up in this group of patients have been published previously.[1,6,7] Similarly, the clinical variables assessed, the methods of their assessment, and the mensuration scales used for each variable have also been published previously.[1] These patients were not assigned to a treatment randomly, but were treated on the basis of tumor size, tumor location, visual status of the involved eye, visual status of the fellow eye, extent of retinal detachment, level of intraocular pressure, age and general health of the patient, and patient preference for a particular treatment. Patients were followed up until

death or their most recent re-examination before the closing date for data analysis (April 1989). Patients who were unable to return to Wills Eye Hospital for periodic follow-up examination at any time in the posttreatment period were advised to undergo periodic re-examination by their referring ophthalmologist and family physician or oncologist. The survival status of these patients was determined by periodically contacting the patients, their family members, or their physicians. Cause of death was determined by contacting the attending physician at the time of death and reviewing, where possible, death certificates and medical records generated during the terminal illness. Patients were considered lost to follow-up if they had not been re-examined at Wills Eye Hospital or by their local physicians within the year before the closing date and if they or a family member could not be located for follow-up by telephone or mail.

Before data analysis, we eliminated those patients who had clinically evident metastatic uveal melanoma before treatment, previous treatment of their tumor, intraocular surgery on the affected eye within the preceding six months, previous uveal melanoma in the fellow eye, or multiple uveal melanomas in the affected eye. One or more of the following clinical variable were also used as bases for elimination: total blindness of the affected eye, severely painful affected eye, extension of the tumor to the optic disk margin or beneath the fovea, clinically detected extrascleral tumor extension, and opaque optical media. These variables were considered to be exclusionary criteria for plaque radiotherapy during the period under study. After these exclusions, 436 patients remained (134 patients in the enucleation group and 302 patients in the cobalt-60 plaque radiotherapy group) for further analysis.

Given the inclusive treatment dates and the closing date for our data analysis, the potential minimum and maximum lengths of follow-up for surviving patients were 64 months and 335 months (almost 13 years), respectively. The median posttreatment follow-up was 7.3 years for the enucleation group and 6.5 years for the cobalt-60 plaque group. Seventeen of the 134 (12.7%) patients in the enucleation group and 14 of the 302 (4.6%) patients in the cobalt-60 plaque group had been lost to follow-up. Only four (3.0%) of the patients in the enucleation group, however, and nine (3.0%) of the patients in the cobalt-60 plaque group were lost to follow-up before five years after their treatment. The median follow-up of the patients lost to follow-up was 6.6 years in the enucleation group and 4.7 years in the cobalt-60 plaque radiotherapy group.

We performed multivariate Cox proportional hazards modeling[8] to identify the best combination of the recorded clinical variables for melanoma-specific mortality in patients treated by primary enucleation. In performing this analysis, we used a comprehensive approach that allowed evaluation of all possible combinations of two and three variables. We considered a model to be satisfactory only if all component variables entered at $P < .01$. Using the beta coefficients derived from this multivariate model, we computed a prognostic index (hazard ratio)[8-10] for each patient in both treatment groups. The prognostic index is a mathematical expression of the likelihood that a particular patient in a group will reach an end point of interest during a specified time interval relative to that of the average patient in the group. The higher the prognostic index for a given patient, the worse the prognosis for survival.

We assessed the similarity of the patients in the two treatment groups with respect to the recorded clinical variables and the computed prognostic indices using the unpaired *t*-test (for continuous numeric variables) and chi-square analysis (all variables). Our nominal significance level for all statistical contrasts was alpha = 0.01. We computed Kaplan-Meier survival curves[11] for the patients in the enucleation and cobalt-60 plaque radiotherapy groups, first using deaths from confirmed metastatic uveal melanoma and then using deaths from all causes as the end point. We compared the corresponding survival curves using the Mantel-Haenszel test.[12] We estimated the relative risk of death per unit time for a patient treated with cobalt-60 plaque radiotherapy vs enucleation by computing the risk ratio for the treatment variable[8] (enucleation coded 1, cobalt-60 plaque therapy coded 2) when it was combined with prognostic index in a multivariate Cox model. For this computation, the risk of death among patients treated by enucleation was the reference category. Consequently, risk ratios less than 1.0 indicated a lower relative risk among patients who underwent cobalt-60 plaque radiotherapy, and risk ratios greater than 1.0 indicated a higher relative risk among patients who underwent cobalt-60 plaque radiotherapy. We performed this analysis twice,

first using death from confirmed metastatic uveal melanoma and then using death from any cause as the end point. We computed 95% confidence intervals for the estimated risk ratios to identify their stability.

Results

We identified a three-term Cox proportional hazards model incorporating largest linear tumor dimension (mean value, 12.6 mm), location of the tumor's anterior margin (mean value, 1.03 [where 0 = posterior to equator, 1 = between equator and ora serrata, and 2 = anterior to ora serrata]), and age of the patient at the time of treatment (mean value, 54.9 years) as the best multivariate regression for predicting melanoma-specific mortality in the complete enucleation group (247 patients). The estimated beta coefficients and significance test results for the clinical variables in this multivariate model are shown in Table 1. All three variables were positively correlated with mortality from metastatic uveal melanoma (that is, the larger the tumor, the more anterior the tumor's peripheral margin, and the older the patient, the worse the prognosis for survival). The ranges of prognostic index values computed from this model for the patients in the two treatment groups were similar, ranging from 0.12 to 6.5 in the enucleation group and from 0.19 to 6.7 in the cobalt-60 plaque radiotherapy group. The median prognostic index of the enucleation group (1.2), however, was higher than that of the cobalt-60 plaque radiotherapy group (0.92).

Comparison of the two treatment groups for the baseline clinical variables (Table 2) showed that patients selected for enucleation were significantly younger and had substantially more symptoms, worse pretreatment visual acuity, more extensive retinal detachment, and larger and more anteriorly located tumors than did patients selected for cobalt-60 plaque radiotherapy. Their tumors also were less likely to be observed for tumor growth than were those in the plaque radiotherapy group. These differences indicated substantial selection bias between the groups.

Despite the highly significant differences between the groups in the three prognostic variables in our multivariate model, the baseline difference between the groups in prognostic index (Table 3) was not statistically significant ($P = .04$, unpaired t-test and chi-square analysis). This apparent paradox exists because the three prognostic variables were not all acting in the same direction: although a substantially greater proportion of patients with unfavorable values of largest linear tumor dimension and location of the anterior tumor margin was present in the enucleation group (Table 2), a substantially greater proportion of patients with unfavorable values of patient age was present in the cobalt-60 plaque radiotherapy group (Table 2). The competing impacts of these simultaneously acting prognostic factors appear to account for the less than expected difference in prognostic index between the groups.

Of the 134 patients in the enucleation group, 57 died before the closing date, including 50 patients with confirmed metastatic uveal melanoma (87.7%), three patients with nonmelanoma malignancy, and four patients who died of causes not related to cancer. In contrast, 113 of the 302 patients in the cobalt-60 plaque radiotherapy group died before the closing date, including 85 patients with confirmed metastatic uveal melanoma (75.2%), eight patients with nonmelanoma cancer, and 20 patients who died of causes not related to cancer. Comparative survival curves for the 134 enucleated patients vs the 302 plaque-treated patients are shown in Figures 1 and 2. The eight-year survival probabilities based on deaths from metastatic uveal melanoma (Fig. 1) were 61.0% (S.E. = 4.5%) for the enucleation group and 67.8%

TABLE 1
ESTIMATED BETA COEFFICIENTS AND SIGNIFICANCE TEST RESULTS FOR THE CLINICAL VARIABLES IN BEST MULTIVARIATE COX MODEL

VARIABLE	BETA COEFFICIENT	STANDARD DEVIATION	*T* VALUE	P
Largest linear tumor dimension	0.109	0.031	3.5	<.001
Location of anterior tumor margin	0.485	0.136	3.6	<.001
Age of patient at time of treatment	0.027	0.008	3.6	<.001

TABLE 2

DISTRIBUTION OF CLINICAL VARIABLES BY TREATMENT GROUP IN 436 PATIENTS WITH POSTERIOR UVEAL MELANOMA

VARIABLE AND CATEGORY	NO. OF PATIENTS (%)		DEGREES OF FREEDOM FOR CHI-SQUARE TEST	CHI-SQUARE OR *T* VALUE*	P
	ENUCLEATION GROUP (N=134)	COBALT-60 PLAQUE RADIOTHERAPY GROUP (N=302)			
Age (yrs)					
≤40	33 (24.6)	29 (9.6)			
>40 to ≤50	21 (15.7)	43 (14.2)			
>50 to ≤60	31 (23.1)	84 (27.8)	4	20.6	<.001
>60 to ≤70	34 (25.4)	83 (27.5)			
>70	15 (11.2)	63 (20.9)			
Mean (range)	52.4 (17–86)	58.7 (26–89)		*t*=4.4	<.001
Sex					
Male	66 (49.3)	151 (50.0)	1	0.002	>.5
Female	68 (50.7)	151 (50.0)			
Symptoms					
Asymptomatic	13 (9.7)	62 (20.5)	1	6.9	.009
Symptomatic	121 (90.3)	240 (79.5)			
Visual acuity					
≥20/40	61 (45.5)	199 (65.9)			
20/50 to 20/100	36 (26.9)	61 (20.2)	2	17.9	<.001
≤20/200	37 (27.6)	42 (13.9)			
Intraocular pressure (mm Hg)					
≤12	43 (32.1)	87 (28.8)			
13 to 16	60 (44.8)	137 (45.4)	2	0.6	>.5
≥17	31 (23.1)	78 (25.8)			
Mean (range)	14.2 (7–31)	14.7 (6–42)		*t*=1.3	.20
Basal tumor diameter (anteroposterior) (mm)					
≤10	35 (26.1)	121 (40.1)			
>10 to ≤15	70 (52.2)	150 (49.7)	2	13.9	.001
>15	29 (21.6)	31 (10.3)			
Mean (range)	12.6 (4.0–22.0)	11.4 (5.0–22.0)		*t*= −3.6	<.001
Basal tumor diameter (circumferential) (mm)					
≤10	45 (33.6)	179 (59.3)			
>10 to ≤15	66 (49.3)	103 (34.1)	2	27.9	<.001
>15	23 (17.2)	20 (6.6)			
Mean (range)	11.7 (3.5–20.5)	10.2 (4.0–20.0)		*t*= −4.5	<.001
Tumor thickness (mm)					
≤5	26 (19.4)	105 (34.8)			
>5 to ≤8	54 (40.3)	125 (41.4)	2	16.0	<.001
>8	54 (40.3)	72 (23.8)			
Mean (range)	7.6 (1.0–16.0)	6.5 (1.5–15.5)		*t*= −4.2	<.001
Largest linear tumor dimension (mm)					
≤10	30 (22.4)	117 (38.7)			
>10 to ≤15	68 (50.7)	150 (49.7)	2	20.7	<.001
>15	36 (26.9)	35 (11.6)			
Mean (range)	13.0 (4.0–22.0)	11.5 (5.0–22.0)		*t*= −4.6	<.001
Location of anterior tumor margin					
Posterior to equator	25 (18.7)	97 (32.1)			
Between equator and ora serrata	51 (38.1)	119 (39.4)	2	12.2	.002
Anterior to serrata ora	58 (43.3)	86 (28.5)			
Location of posterior tumor margin (relative to optic disk [mm])					
≤3	27 (20.1)	72 (23.8)	1	0.53	.5
>3	107 (79.9)	230 (76.2)			
Activity of tumor					
Growth not documented	128 (95.5)	255 (84.4)	1	9.7	.002
Growth documented	6 (4.5)	47 (15.6)			
Retinal detachment					
None	17 (12.7)	70 (23.2)			
>0 to ≤50%	70 (52.2)	175 (57.9)	2	15.9	<.001
>50%	47 (35.1)	57 (18.9)			
Mean (range)	34.1 (0–100)	22.7 (100)		*t*= −4.3	<.001

*T statistic for comparison of means is shown only for variables recorded on a continuous numeric scale.

(SE. = 3.1%) for the cobalt-60 plaque radiotherapy group. The difference between these survival distributions is not statistically significant (P = .25, Mantel-Haenszel test). The eight-year survival probabilities based on deaths from all causes (Fig. 2) were 57.5% (S.E. = 4.5%) for the enucleation group and 60.0% (S.E. = 3.1%) for the cobalt-60 plaque radiotherapy group. The difference between these survival distributions also lacks statistical significance (P = .89, Mantel-Haenszel test).

The risk ratio for the treatment differential was estimated to be 0.90 when death from metastatic melanoma was the end point and 1.06 when death from any cause was the end point. These risk ratios, which are nearly equal to 1.0, indicate an essentially equivalent risk of death within a given time period for patients with identical prognostic index treated by cobalt-60 plaque radiotherapy vs enucleation. The 95% confidence intervals for these ratios were found to range from 0.63 to 1.29 for the ratio based on melanoma-specific mortality and from 0.68 to 1.31 for the ratio based on deaths from all causes. Because these intervals include the value 1.0, the difference between the treatments is not statistically significant.

Discussion

The results of our nonrandomized but statistically adjusted survival study of patients with a primary choroidal or ciliary body melanoma treated by enucleation or cobalt-60 plaque radiotherapy suggest these treatments are nearly equivalent in their impact on survival during the first eight posttreatment years. These results provide no compelling evidence that enucleation is substantially more effective than cobalt-60 plaque radiotherapy in preventing death from metastatic uveal melanoma.

This study has strengths as well as weaknesses. The principal strength of our study is that baseline clinical variables were assessed in all patients in both treatment groups according to a standardized protocol. This prospective assessment of baseline clinical variables ensures that measurement bias[13] (the situation that would occur if the size of posterior uveal tumors were estimated clinically in one group and measured by pathologic specimens in the other group) and diagnosis bias (the situation that would occur if the diagnosis of posterior uveal melanoma were made clinically in one group and pathologically in the other group) did not influence the survival comparisons. A second strength of our study was the use of multivariate Cox proportional hazards modeling[8] to adjust statistically for recognized intergroup differences in baseline prognostic clinical variables.

The principal weakness of our study is that the treatment decision for patients in the two groups was not randomized. As a consequence of the nonrandomized treatment assignment, our patient groups proved to be substantially dissimilar in multiple baseline clinical variables (including the three prognostic factors identified by our multivariate analysis). This selection bias strongly suggests the presence of susceptibility bias[14] (an unequal baseline susceptibility of the groups to the outcome event of interest, which in this study was death from metastatic uveal melanoma). Bias of this type may have masked a true treatment differential in this study. Although multivariate Cox modeling minimizes the impact of recognized selec-

TABLE 3
DISTRIBUTION OF PROGNOSTIC INDEX IN 436 PATIENTS WITH CHOROIDAL OR CILIARY BODY MELANOMA

PROGNOSTIC INDEX	NO. OF PATIENTS (%) ENUCLEATION GROUP (N=134)	NO. OF PATIENTS (%) COBALT-60 PLAQUE RADIOTHERAPY GROUP (N=302)	DEGREES OF FREEDOM FOR CHI-SQUARE TEST	CHI-SQUARE OR *T* VALUE*	P
≤0.7	35 (26.1)	109 (36.1)	2	6.4	.04
>0.7 to ≤1.25	44 (32.8)	103 (34.1)			
>1.25	55 (41.0)	90 (29.8)			
Mean (range)	1.5 (0.12–6.5)	1.3 (0.19–6.7)		$t = -2.0$	.04

*T statistic for comparison of means is shown only for variables recorded on a continuous numeric scale.

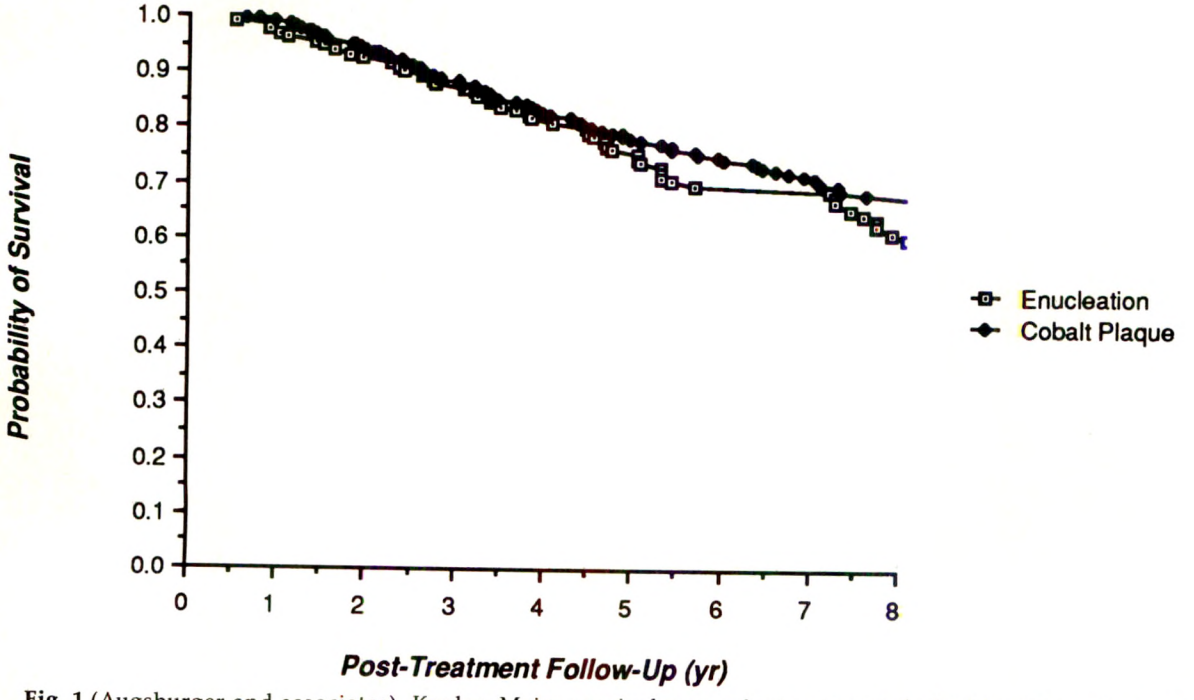

Fig. 1 (Augsburger and associates). Kaplan-Meier survival curves by treatment method for 134 patients with primary choroidal or ciliary body melanoma treated by enucleation and for 302 patients treated by cobalt-60 plaque radiotherapy. These survival curves are based on deaths from metastatic uveal melanoma only. Patients who died of other causes contributed survival data only until the date of death. The difference between these curves is not statistically significant (P = .25, Mantel-Haenszel test).

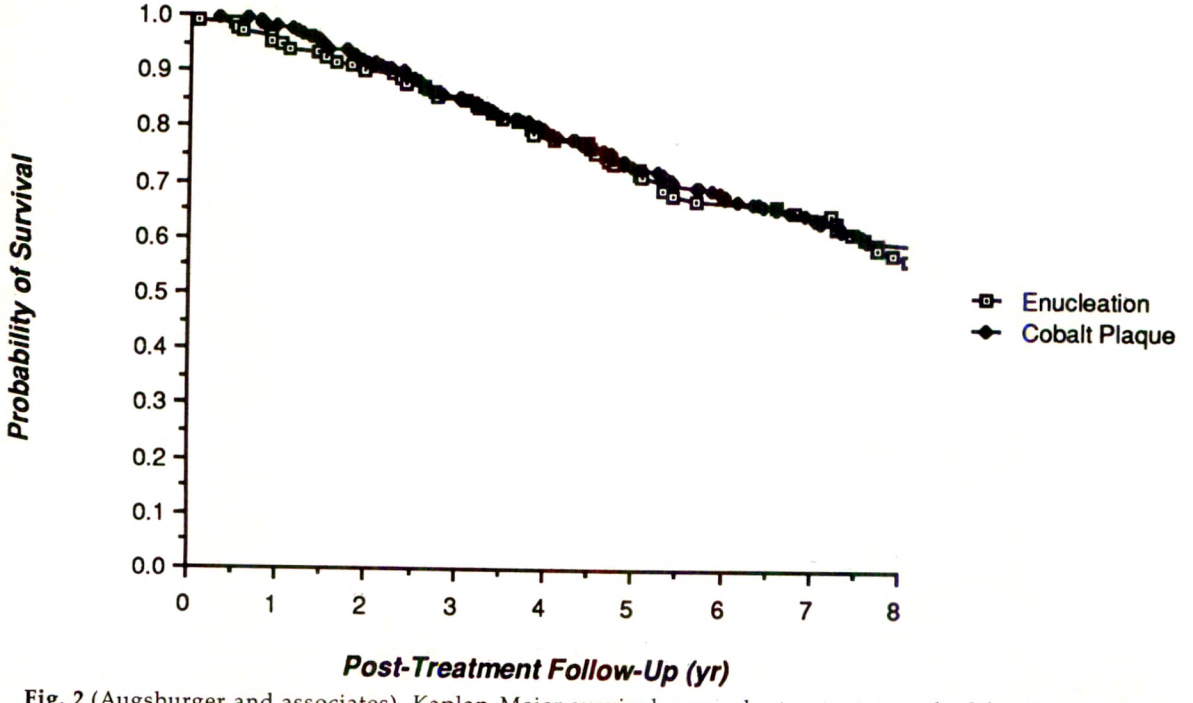

Fig. 2 (Augsburger and associates). Kaplan-Meier survival curves by treatment method for 134 patients with primary choroidal or ciliary body melanoma treated by enucleation and for 302 patients treated by cobalt-60 plaque radiotherapy. Unlike the curves in Figure 1, these survival curves are based on deaths from all causes. The difference between these curves is not statistically significant (P = .89, Mantel-Haenszel test).

tion bias, this statistical adjustment method does not correct for unrecognized bias. A second weakness of our study is the possibility of detection bias[14] (an inequality between the groups in detection of the outcome event) regarding the cause of death. We have no assurance that the causes of death were ascertained with equal accuracy in both treatment groups. It is thus bothersome that almost 88% of the deaths in the enucleation group but only 75% of the deaths in the cobalt-60 plaque group were classified as attributable to metastatic uveal melanoma. Our comparative survival analysis using deaths from all causes as an alternative end point addresses this problem to some degree; if detection bias were a major factor, this analysis based on total mortality would be expected to minimize the impact of that bias. A third weakness of our study is one of transfer bias[14] (an inequality between the groups in completeness of follow-up). There was a substantially higher proportion of patients lost to follow-up in the enucleation group, for which no statistical manipulation of the data can compensate. We have recently submitted an application to the National Death Index in an effort to obtain mortality information on the lost patients. A fourth limitation of this study is the relatively small number of patients in each group. Because of the limited number of patients and the relatively small proportion of patients who died of metastatic uveal melanoma during the posttreatment period, one must interpret the results of our comparative survival analysis as inconclusive rather than negative.[15]

One might assume from this study that our group still uses cobalt-60 plaques on a regular basis. This is not the case. We started using alternative plaques (ruthenium 106, iridium 192, and iodine 125) for selected patients with posterior uveal melanoma in 1982 and have recently switched almost exclusively to shielded iodine-125 plaques. Iodine-125 plaques appear to have several practical and theoretical advantages over cobalt-60 gamma-emitting plaques, and these advantages have been summarized in detail.[16] Because most of our experience with eye-preserving treatment of choroidal and ciliary body melanomas has been with cobalt-60 plaques and because we anticipate no substantial difference in local tumor control rates and systemic cure rates with iodine 125 vs cobalt 60, we believe that these cobalt-60 plaque vs enucleation results are likely to be reasonable approximations of what may be expected in our iodine-125 plaque vs enucleation study. We believe that all patients with a primary posterior uveal melanoma who are candidates for plaque radiotherapy or enucleation should be informed of these results and advised of their implications regarding survival.

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PERSPECTIVES

The Oversupply of Ophthalmic Practitioners

Joseph C. Noreika, M.D.

Critics of the medical profession have long pointed to medicine's cartel-like organization as a primary cause of accelerating health-care costs. By maintaining high barriers to entry by means of difficult and lengthy training programs, licensures, certifications, and the legislative umbrella that safeguards the system, it is argued that physicians can sustain their prices at artificially high levels because demand for health care has traditionally outstripped the carefully regulated supply of providers. I believe these suppositions are no longer valid and provide demographic data and trend analysis to support my argument.

There were 15,180 ophthalmologists in the United States at the end of 1986.[1] Ninety-seven percent of these ophthalmologists were involved in office-based, direct patient care. There were 1,955 ophthalmologists in training programs or, approximately, one ophthalmologist in training for every five ophthalmologists in office-based patient care. At the end of 1976, there were 11,455 ophthalmologists. Ophthalmology has witnessed a 33% increase of specialists involved in direct patient care between 1976 and 1986. The percentage of ophthalmologists in training programs remained the same.

At the end of 1986, 53% of all ophthalmologists were younger than 45 years of age. The largest age cohort (30%) includes ophthalmologists who were 35 to 44 years of age. Although only 8% of all ophthalmologists were women, 50% of these women were under 35 years of age.

Between 1983 and 1987, male U.S. medical students have demonstrated an increasing interest in the surgical subspecialties. Women's interest in the subspecialties has remained constant over the same years.[2] There is also much greater interest in surgical subspecialization

among premedical students, both men and women, than previously.[2]

Data supplied by the office of the Ophthalmology Matching Program for the years 1984 to 1990 disclosed the following: the number of applicants for ophthalmology residency position openings in 1990 was 816, down from a peak in 1987 of 1,045. This represents a 22% decrease in applications for ophthalmic residency positions. In 1987, 55% of applicants gained admission to a residency program. In 1991, 75% of applicants will gain positions. The most recent residency match saw more older applicants, many from other medical fields, and more foreign medical graduates accepted. Although data are not available about male:female ratios, sources report that significantly more women are being accepted into residency programs.

Since 1979, the number of accredited residency programs has decreased from 163 to 137, which is a 16% decrease.[3,4] According to data from the Ophthalmology Matching Program, the number of first-year (postgraduate year 2) ophthalmology residency positions has increased by 2% since 1984 to a total of 477 openings. Other data yield slightly different numbers over the last decade, from a low of 454 first-year ophthalmology residency positions in 1982 to a high of 527 in 1986 (increase, 16%) with 507 filled first-year openings in 1987.[5]

Correspondingly, the American Optometric Association disclosed that there are approximately 25,900 optometrists practicing in the United States. There are approximately 5,000 students in optometry schools currently, and it is estimated that 90% will finish training. Last year, 1,200 optometrists entered practice. Whereas there were 8.9 optometrists per 100,000 people in 1973, there are now 10.3 per 100,000 today with an expected increase to 11.3 by the year 2000. At 40 years of age, the median age of optometrists today is ten years younger than it was in 1977.

Some believe that more ophthalmologists will ensure better distribution of ophthalmic care. The same percentage (89% vs 88%) of ophthalmologists preferred to practice in metropolitan areas in 1986 as 1976. Ophthalmologists, like everyone else, want to work and live in attractive areas. Additionally, the data indicate that the number of first-year residency positions in ophthalmology has increased while the number of training programs has declined. Possibly this indicates greater geographic concentration of residency training programs. Because physicians often begin practice in close proximity to where they were trained, this concentration of training programs may work against better distribution of practitioners.

Some assume that more ophthalmologists will be needed to fulfill the demand of an aging population. The increase in the number of older people will be less in the next 20 years, however, than it was in the last 20 years. Since 1970, the number of people 65 years of age and older increased by 11.5 million. From now to 2010, the increase will be only 7.8 million people, which is a 32% decrease.[6] Relatively fewer babies were born during the Great Depression and World War II, which accounts for this demographic aberration. The baby-boomers will not turn 65 until the year 2011. Although people 85 years of age and older will remain the fastest growing age cohort, their actual numbers are small relative to the general population. When health-care rationing becomes a reality in this country, other countries' experience suggests that the oldest citizens will be most affected, and their proportional claim on the health-care dollar will diminish.

Some ophthalmologists believe that more sophisticated technology, such as photorefractive keratectomy, will provide an enormous increase in demand for ophthalmic services. Photorefractive surgery, however, is at least three years away from wider dissemination, and it is unknown when the Food and Drug Administration will deem it safe for general use. The potential market involves billions of dollars. However, it is not clear and it is unlikely that ophthalmology will be permitted to monopolize this technology once approved. Because of new eye-tracking technology used in its solid-state lasers, according to one laser manufacturer, "we're taking the surgeon's skill, or lack of it, out of the equation."[7] Optometry is posed to play a significant role in the provision of photorefractive surgery, and if the technology's early promise is realized, it may be difficult to convince legislators and regulators that only ophthalmologists will be capable of providing this treatment. Other important but less newsworthy technology may not be as readily available to ophthalmologists as the government attempts to restrict its diffusion as a means of holding down health-care demand and cost.[8]

Some ophthalmologists believe that they will always enjoy a professional advantage over optometrists and thereby retain their status at the top of the eye-care hierarchy. Organized

optometry, however, has won the right to treat patients with therapeutic drugs in half of the United States with bills currently pending in other state houses. Lobbyists for organized medicine have indicated that it is unlikely that physicians will be able to block the persistent and well-focused efforts of so-called limited practitioners from expanding their scope of practice. The optometric literature indicates that laser therapy is the next target for organized optometry's legislative efforts.[9] Additionally, optometrists are becoming more important in patient care in managed health-care organizations. As long as cost of care drives the system, the less costly professional will be used more frequently in the primary care of patients.

Some believe that even if more ophthalmologists are available, the excess will be absorbed by corporate health-care providers such as health maintenance organizations and large, multispecialty group practices. However, health maintenance organizations need fewer specialists, including ophthalmologists, to care for their patients than those required by the current fee-for-service sector.[10] More ophthalmologists may be forced to seek employment in managed care organizations, but it is impossible to estimate the availability of these positions or the quality of professional and career opportunities offered. Because large, multispecialty group practices face the same fiscal constraints as health care in general, it is not logical to expect a meaningful increase in their ophthalmic practitioner needs.

It is said that the morale of physicians is at an all-time low and that many ophthalmologists will choose early retirement. Historically, however, excess capacity in medicine has left the system slowly. Although many ophthalmologists talk about early retirement, the young average age of the practitioners and the realities of home mortgages, college educations for children, and the ever-threatening inflationary erosion of retirement dollars keep physicians working. Even the burgeoning industry of health-care administration cannot be expected to absorb all the available physicians seeking to leave patient care. Only 23% of ophthalmologists are 55 years of age and older. As of 1986, there were 1,372 practitioners (9.3%) 65 years of age and older involved in patient care. With nearly 1,500 ophthalmologists in training in 1989, a large percentage of older ophthalmologists could retire and not significantly affect the overcapacity of the profession.

My intent is not to propagate the town vs gown controversy, which dates back to at least the last century.[11] In light of the evidence, it can be argued that the American Academy of Ophthalmology and the American Association of University Professors of Ophthalmology must work to reduce significantly the supply of new ophthalmic practitioners.

An increased number of practitioners per capita is associated with a decrease in real dollars per physician, and it is plausible that the remuneration expectations of ophthalmologists (that is, their expected return on investment of the human capital of their education and training) will not be met.[12] The real yearly and hourly net income of young physicians deteriorated between 1974 and 1986, whereas annual hours worked increased.[13] I choose, however, to restrict my arguments for the reduction of ophthalmic training opportunities to less self-serving concepts, specifically, the cost and quality of health care.

Each new ophthalmologist can be expected to add millions of dollars to the aggregate health-care bill over the course of that individual's career. It has been shown that the relationship between demand, supply, and price in standard economic theory does not hold for medical services.[14] Physicians do control the total and marginal demand for care because they, as agents for their patients, determine the amount and type of service required. As long as third-party reimbursement shields them from the need for decision-making in terms of their care and its cost, patients have little incentive to become more informed about their choices.

Of course, both physician control and patient incentive are now changing. Ultimately, there are two strategies by which the accelerating costs of health-care can be restrained. One strategy is based on the supply-side and implies limitations on the availability of service as seen in the Canadian and British models in which the diffusion and availability of new technology is restricted and the wait for hospital beds, operating rooms, and elective procedures may be months, or even years. The other strategy addresses the demand-side of health care and denotes capitation of dollars available for services rendered. It appears that recent legislation in the United States, such as Medicare's volume performance standards, favors the latter approach. It remains to be seen if American physicians will accept the responsibility of telling their patients, as Uwe Reinhardt has eloquently put it, "There's an empty bed. There's a machine. There's an idle surgeon. But the bud-

get is limited; therefore, go away.''[15] Either situation requires fewer medical specialists than exist in the current American system with its apparent lack of fiscal and technologic limits.

By considering the expansion of ophthalmic training programs to four years, the Association of University Professors of Ophthalmology has implicitly and, perhaps, unknowingly admitted that the quality of training ophthalmic residents currently receive is less than adequate.[16,17] Even if the Association proceeds with plans to lengthen the training period, it will have done nothing to effectively relieve the practitioner glut, because the total number of ophthalmologists produced will not significantly change.

Whether the prospects of longer residencies and decreased future remuneration will influence the quality of applicant seeking ophthalmic training is unknown. Medical schools, however, have seen the academic qualifications of candidates fall, and fewer medical students are interested in ophthalmology. The competition to secure a residency position has diminished markedly. Perhaps ophthalmology's well-publicized difficulties within and without the medical community are known to medical students. This could explain why premedical and medical students appear to have less interest in ophthalmology even though interest in surgical subspecialty training in general has risen. With its future prospects, it is unclear whether ophthalmology can continue to recruit the best and the brightest.

Postgraduate training may have less effect on the skill of clinicians than the lack of application of those skills once in practice. The pool of potential cataract patients will decrease over the next 20 years. Fewer surgeons will have the opportunity to refine the skills learned in residency, and the skills may decay with disuse. Studies have shown that surgical experience is a most critical statistical parameter defining surgical mortality.[18,19] Learning-curve theory leads one to expect a positive correlation between volume of surgery and outcome, especially as the sophistication of today's technology grows.

There is great concern about medical ethics today. Increased competition,[20] the monetarization of health care,[21] and the medical-industrial complex[22] have led some ophthalmologists to test the limits of professional standards and responsibility. Coincidentally, public opinion of physicians as a group has fallen dramatically. With an ever-increasing number of ophthalmologists fighting for a rapidly shrinking portion of the health-care dollar, competition will continue to escalate, and the temptations to cut corners in clinical practice may intensify. The ethical standards of the health-care industry are ultimately defined by the ethical standards of its physicians. Future erosion in medical ethics will be the product of the system's excess capacity. The adverse effect on the trust in the doctor-patient relationship, which is necessary for its inherent healing power, may be the greatest cost to physicians as the deprofessionalization of medicine continues.[23] Quality of care must suffer as a consequence.

The surplus of ophthalmologists is the single most important issue facing the profession today. Ophthalmology will need strong and courageous leadership from the American Academy of Ophthalmology and the American Association of University Professors of Ophthalmology and cooperation and support from the American Medical Association if we are to avoid the potentially dire consequences of our current policy.

During the days of Lyndon Johnson's ''Great Society,'' the government mandated an enormous increase in physicians. Armed with the legal ruling of Goldfarb v. Virginia State Bar, which decreed that professions were not exempt from the Sherman Antitrust Act, thereby establishing medicine's status as a trade and promoting competition as a restraint to escalating physician fees, the Federal Trade Commission has zealously policed any attempts by organized medicine to set limits on the number of its practitioners to the point where the issue cannot be discussed in open forum without fear of antitrust law violation. This is not to excuse our leadership, however, from its responsibilities.

It is disconcerting that our ophthalmic leadership cannot openly question and investigate the existence and scope of the problem without the threat and fear of being accused of taking an anticompetitive stance by the Federal Trade Commission. The costs of antitrust litigation with its intrusiveness, drawn-out proceedings, and treble damages is enough to give anyone pause. Only when the issues raised here can be debated in open forum and a profession-wide dialogue can be established among our leadership will the significance of these concerns be delineated.

There may be a political window of opportunity. Some legislators and their advisors have finally recognized the definitive effect of increasing physician supply, mainly, increased use of the system with attendant rise in costs.

An influential member of the Physician Payment Reform Commission has stated that the excess capacity in health care is the fundamental reason for accelerating costs.[24] Americans find that they cannot pay for or choose not to pay for the physicians their government has provided. Political opinion of the current health-care environment may now favor open study of ophthalmology's predicament. Legislators may be more inclined to allow candid discussion without threat of legal retaliation and retribution. We must attain safe-harbor status for deliberation on these concerns. Because this can be achieved only with the support of informed legislators, ophthalmologists and, especially, younger eye-care providers must become involved in grass-roots efforts to influence their elected federal representatives. Although our leadership can be expected to spearhead this effort, they are absolved of any duty to do so if the cooperation, energy, and resolve of their constituents are found lacking.

I believe that a significant reduction in the number of ophthalmic residency programs and training positions is necessary. As a physician, I do not propose forfeiture of our responsibility to educate; I argue for quality over quantity. The profession demands that issues of ego, position, power, competitive advantage, and economic self-interest implicit in this crisis be set aside for an egalitarian vision of the collective future of our profession. Just as American industry found that downsizing and improving efficiency involve both crisis and opportunity, ophthalmology and its leaders have a mandate to train fewer and better ophthalmologists.

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LETTERS TO THE JOURNAL

Excretion of Fluorescein Into Breast Milk

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Fluorescein is widely used to study blood-retinal and blood-aqueous permeability, corneal integrity, and ocular disease states. Fluorescein pharmacokinetics have been reported in humans, especially after systemic administration.[1,2] However, there is no information regarding plasma fluorescein concentrations after topical instillation or in nursing women. Since many drugs in the maternal circulation may be excreted into breast milk and administered to a breast-fed infant, an estimate of the potential for delivering fluorescein to the child is needed. We monitored plasma and breast milk concentrations of fluorescein after a single topical ophthalmic dose to a nursing mother.

A 28-year-old woman delivered a healthy baby boy after a normal gestation period. This study was conducted three months after the birth while the son was being nursed. Nursing was curtailed for the day of the study. Fluorescein sodium ophthalmic solution, 2.0%, was administered topically to both eyes of the lactating mother. Three blood and breast milk samples of 5 ml each were taken every 30 minutes after drug instillation for analysis. Results of ocular examinations performed before and after the study were normal. Fluorescein concentrations in plasma and breast milk were analyzed with a scanning fluorophotometer; the sensitivity of the instrument is 1 ng/ml. Plasma fluorescein concentrations at 45 and 75 minutes after dose were 36 and 40 ng/ml, respectively. Fluorescein breast milk concentrations at 30, 60, and 90 minutes were 20, 22, and 15 ng/ml, respectively. Zero time controls for both plasma and breast milk contained no measurable fluorescein.

Though the sampling schedule was limited, it appears that fluorescein concentrations are fairly consistent in plasma and breast milk over this short time interval, even though fluorescein has a short, 2- to 3-hour half-life.[3] Because of the absorption kinetics, a drug may demonstrate similar plasma concentrations around the peak time after extravascular administration. Because breast milk concentrations reflect plasma concentrations, it is not unexpected to obtain consistent breast milk concentrations over nearly the same time interval. The breast milk concentrations, one-half the values observed in plasma, may occur because of the relatively nonpolar nature of the compound. The drug is known to cross into the placenta.[4]

A potential error may occur in the study because the assay method measures fluorescein glucuronide as well as the parent compound. Fluorescein is rapidly metabolized to its conjugate systemically such that comparable concentrations are achieved within an hour of oral or intravenous administration.[3,5] However, the ratio of fluorescent intensities for fluorescein and fluorescein glucuronide is 8:1.[1] Therefore, at

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these early time points, it is reasonable to expect that a significant amount of the drug measured is intact fluorescein.

We believe topical ocular fluorescein is absorbed systemically and crosses into a mother's breast milk. Even though fluorescein has low potential for toxicity, these data suggest that a nursing mother should be notified not to breast feed for 8 to 12 hours after topical fluorescein administration. These findings become more important when a hundredfold larger oral or intravenous dose of fluorescein is administered to a patient. An assessment of the benefit to the mother and risk to the infant should be undertaken in each individual case.

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Repair of a Leaking Bleb With Fibrin Glue

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A postoperative regimen of daily subconjunctival injections of 5-fluorouracil markedly improved the success rate of filtering operations in patients with intractable glaucoma.[1] In addition to the adverse effects on the corneal epithelium,[2] the inhibitory effect of 5-fluorouracil on conjunctival wound healing may lead to aqueous leakage and the collapse of the anterior chamber.[3] I used fibrin glue to close a dehisced conjunctival wound through which slight aqueous leakage persisted despite resuturing.

A monocular 67-year-old woman with uncontrollable glaucoma underwent an uncomplicated trabeculectomy through a corneoscleral limbus-based conjunctival flap. A 9-0 silk running suture was used for conjunctival wound closure. On the first postoperative day, the anterior chamber was maintained by injected sodium hyaluronate. The intraocular pressure, as measured by applanation tonometry, was 5 mm Hg. A regimen of daily subconjunctival injections of 5-fluorouracil was begun. Intraocular pressure on the second postoperative day was 2 mm Hg, with no wound leakage detected on Seidel testing. On the third postoperative day, the anterior chamber was flat. Seidel testing showed slight but continuous leakage through the conjunctival wound and suture holes. Despite successful resuturing with no leakage on the sixth postoperative day, the anterior chamber collapsed again on the next day, also with slight but continuous leakage. A pressure patch was only effective in anterior chamber formation while it was being applied. The patient complained of the complete blindness resulting from eye patching, so it was decided that the wound should be sealed by some other method.

On the eighth postoperative day, cyanoacrylate was applied from a 27-gauge needle over the conjunctival wound. After 5 minutes, the filtering bleb had expanded; 20 minutes later, increased depth of the anterior chamber was noted. The next morning, however, coagulated cyanoacrylate was found to have spontaneously detached in a thin plate, and again the anterior chamber had collapsed. Another attempt was made, which also resulted in failure. On the 13th postoperative day, fibrin glue was applied over the wound after the conjunctiva had been dried as much as possible. Fibrinogen solution and thrombin solution were then applied, three times each, alternately, from a 27-gauge needle tip (Fig. 1, left). I used Beriplast P (Hoechst Japan, Behring Welke AG), which includes highly condensed fibrinogen and thrombin solutions reinforced with factor XIII and aprotinin. No leakage was detected by Seidel testing, and the depth of the anterior chamber increased within half an hour. The next morning, the anterior chamber was as deep as in the

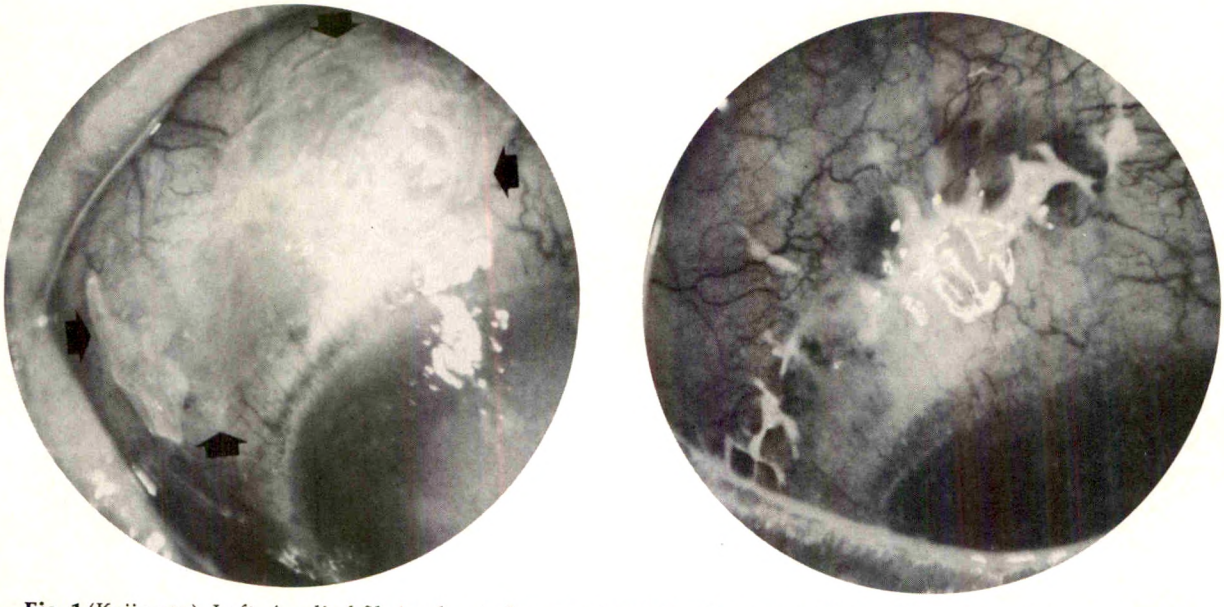

Fig. 1 (Kajiwara). Left, Applied fibrin glue is fluorescein-stained (arrows). Right, The extent of the applied glue was reduced over the time course, but wound dehiscence and suture holes were firmly sealed, without leakage, on the 19th postoperative day.

preoperative state, and an exuberant, diffuse bleb was noted. The extent of the applied fibrin glue gradually reduced over the time course (Fig. 1, right), possibly because of physical abrasion by eyelid movement, but the wound itself was firmly sealed. The patient was discharged on the 15th postoperative day with an anterior chamber of normal depth (Fig. 2) and no aqueous leakage. The intraocular pressure was kept at 5 to 6 mm Hg for the next ten months.

Cyanoacrylate was successfully used by Grady and Forbes[4] in the repair of fistulas after glaucoma surgery. In my patient, however, an attempt to arrest wound dehiscence with cyanoacrylate failed twice. This was possibly because of failure to accomplish complete dryness before application. After a filtering operation, it is almost impossible to dry the wound edges, suture holes, and surrounding tissue completely because of aqueous leakage. In contrast, fibrin glue can coagulate even in wet conditions, as Zauberman and Hemo have reported,[5] and has a longer sealing effect with the tissue after coagulation. It has been applied as a physiologic tissue glue to prevent postoperative fluid leakage and oozing hemorrhage after neurosurgery, lung surgery, cardiovascular surgery, and other surgical procedures. Additionally, human-derived fibrinogen is less irritative to the tissue.

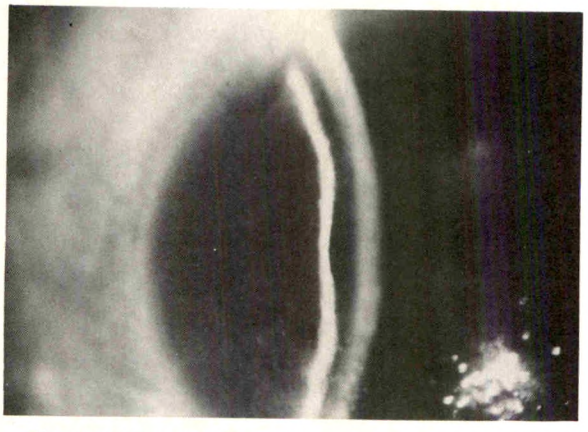

Fig. 2 (Kajiwara). The patient was discharged with a normal-depth anterior chamber and intraocular pressure of 5 mm Hg.

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Inhibition of Exercise-Induced Pigment Dispersion in a Patient With the Pigmentary Dispersion Syndrome

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Pigmentary dispersion syndrome is thought to result from the rubbing of the iris pigment epithelium on the anterior packets of zonules.[1] Strenuous exercise may precipitate episodes of pigment dispersion in some patients.[2,3] We treated a patient who consistently developed pigment dispersion and increased intraocular pressure after playing basketball. Both the pigment dispersion and the pressure rise could be inhibited by treatment with topical 0.5% pilocarpine before exercise.

A 29-year-old myopic man had blurred vision and halos around lights after playing basketball. Slit-lamp examination showed Krukenberg spindles, midperipheral iris transillumination defects, and marked pigmentation of the trabecular meshwork in both eyes. The optic disks and visual fields were normal.

After obtaining informed consent, we examined the patient 30 minutes before and 30 to 60 minutes after strenuous exercise (playing basketball for approximately two hours) on several different days. Intraocular pressure was measured by pneumotonometry, and anterior chamber pigment was graded on a modified Mitsui scale.[4] There was no pretreatment for the initial trial. Intraocular pressure was R.E.: 19 mm Hg and L.E.: 21 mm Hg before exercise with trace anterior chamber pigment in both eyes. After exercise, intraocular pressures increased to 47 mm Hg in both eyes with severe anterior chamber pigment. In subsequent trials either the left eye only or the right eye only was treated with 0.5% pilocarpine (one drop 30 minutes before exercise) or 0.5% thymoxamine (one drop 1½ hours and 30 minutes before exercise). When either eye was pretreated with pilocarpine, the intraocular pressure actually decreased after exercise in the treated eye, and there was minimal or no increase in anterior chamber pigment. When either eye was left untreated or was pretreated with thymoxamine, a marked increase in both intraocular pressure and anterior chamber pigment (similar to that seen in the initial trial) occurred after exercise.

In two previously reported cases of symptomatic pigment dispersion,[2,3] both patients described symptoms that most commonly occurred after playing basketball. One patient was given pilocarpine to use prophylactically. This reportedly relieved the symptoms, but it is not clear whether it inhibited pigment release or intraocular pressure increase since no measurements were made just before exercise.[3] Our patient also exhibited pigment dispersion and intraocular pressure increase after 90 minutes of jumping exercises but not after comparable periods of jogging or bicycling. Jumping exercises may be more likely to cause iris-zonule contact.

In our patient, 0.5% pilocarpine clearly inhibited exercise-induced dispersion of pigment and increase in intraocular pressure while 0.5% thymoxamine (an alpha adrenergic inhibitor) did not. Though pilocarpine increases aqueous outflow and thus lowers intraocular pressure, this mechanism would not explain inhibition of pigment release. The greater pupillary constriction achieved with pilocarpine may more effectively inhibit iris-zonule contact. Pilocarpine may be clinically useful when given prophylactically before exercise in patients subject to exercise-induced pigment dispersion.

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The Influence of Residual Methylcellulose Solution on Tono-Pen Readings

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It is important to perform tonometry after argon laser trabeculoplasty to detect transient, but potentially dangerous increases in intraocular pressure.[1] Although Goldmann applanation tonometry is used commonly, the Tono-Pen tonometer is becoming increasingly popular because it is portable and relatively easy to use.[2-5]

We have observed falsely increased intraocular pressure measurements and have occasionally encountered eyes in which we were unable to obtain a measurement at all with the Tono-Pen after argon laser trabeculoplasty. We investigated the cause of the falsely increased measurements with the Tono-Pen as compared to Goldmann applanation tonometry in 30 patients with chronic open-angle glaucoma who underwent argon laser trabeculoplasty.

The eyes treated with argon laser trabeculoplasty were carefully wiped with a clean tissue after instilling one drop each of 0.5% betablocker (betaxolol, levobunolol, or timolol) and 0.1% fluorometholone, and wiped once more after instillation of one drop of 0.5% proparacaine containing 0.25% fluorescein. The intraocular pressures were measured first with a calibrated Goldmann applanation tonometer. Consecutive Goldmann measurements were made on each eye until two readings were within 1 mm Hg of each other; these were averaged. Tono-Pen tonometry was then immediately carried out to obtain two measurements of the highest reliability (variance of 5% or less); the two readings were averaged. Despite repeated attempts in three patients, Tono-Pen readings with the highest reliability could not be obtained in the eyes treated with argon laser trabeculoplasty.

In the remaining 27 eyes treated with argon laser trabeculoplasty, the Tono-Pen readings were significantly higher than those with Goldmann tonometry (27.9 ± 7.1 vs 21.9 ± 6.3 mm Hg, $P = .0001$ by two-tailed, paired t-test). Thorough washing of the eyes treated with argon laser trabeculoplasty free of residual methylcellulose was performed by profusely irrigating with normal saline. This caused a significant decrease in intraocular pressure measurements by the Tono-Pen, but not Goldmann, which resulted in a close agreement between the Tono-Pen and Goldmann readings (20.7 ± 5.1 vs 20.4 ± 5.7 mm Hg, $P = .311$). There was no statistically significant difference between Tono-Pen and Goldmann applanation tonometries in the fellow eyes that had neither argon laser trabeculoplasty nor methylcellulose instillation (18.2 ± 3.5 vs 18.2 ± 3.8 mm Hg, $P = .899$).

The residual methylcellulose must be the cause of the falsely increased intraocular pressure measurements by the Tono-Pen in the eyes treated with argon laser trabeculoplasty. Additionally, the presence of methylcellulose solution made obtaining intraocular pressure measurement by the Tono-Pen more difficult, and, in three glaucoma patients, even impossible despite repeated attempts. It is reassuring to confirm that Tono-Pen tonometry is reliable in the fellow eyes without the use of methylcellulose and even in the eyes treated with argon laser trabeculoplasty after a thorough irrigation of methylcellulose from the eyes.

Although we only studied the effects of methylcellulose solution on the accuracy of the Tono-Pen readings, it is important to consider that the Tono-Pen results may also be affected by other topical agents that affect the tear film viscosity.

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Epidermal Growth Factor in Human Aqueous Humor

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Corneal endothelial cell loss and dysfunction have been reported in association with ocular surgery, corneal dystrophies, contact lens use, glaucoma, and many other acquired, inherited, and inflammatory conditions. Augmentation of human corneal endothelium by exposure to the mitogen, epidermal growth factor, is the goal of several current investigations. Epidermal growth factor receptors are present on human corneal endothelial cells,[1] and in vitro epidermal growth factor enhances the endothelial cell growth rate (nonhuman studies) and alters cell morphology.[2] Some investigators have demonstrated human endothelial cell division when epidermal growth factor is added to corneal storage media,[3] and on this basis epidermal growth factor supplemented media are being tested.

We used a highly sensitive and specific radioimmunoassay to determine levels of epidermal growth factor in human aqueous. After giving informed consent, patients undergoing intraocular surgery at our institution were included in this study. Blood was drawn from all patients into vacuum tubes within one hour before surgery and placed in an ice water slurry for assay of epidermal growth factor levels in serum and plasma. A 27-gauge needle on a 1-cc syringe was introduced into the anterior chamber at the time of surgery through a standard, partial-thickness surgical wound and at least 100 μl of aqueous was aspirated. The sample was immediately placed on dry ice until it could be transferred to a −80 C freezer.

Epidermal growth factor levels were determined by radioimmunassay wherein ^{125}I-labeled recombinant human epidermal growth factor competes with any unlabeled epidermal growth factor in the sample for a limited number of monoclonal antibody binding sites. The bound and unbound epidermal growth factor was separated using a protein A-conjugated goat anti-mouse antibody. No crossreactivity of this assay was found against platelet-derived growth factor, transforming growth factor alpha, fibroblast growth factor, or insulinlike growth factor-1. The assay is sensitive to 500 pg of epidermal growth factor per milliliter. The competitive binding curve is nonlinear below this concentration (Table).

All of the eyes had intraocular pressures less than 20 mm Hg, except the patient with glaucoma. Measurable epidermal growth factor levels were found in 12 of 15 aqueous samples. In ten of these 12 samples the aqueous level exceeded that of the serum; the aqueous level is greater

TABLE

EPIDERMAL GROWTH FACTOR LEVELS IN HUMAN AQUEOUS, SERUM, AND PLASMA

	EPIDERMAL GROWTH FACTOR CONCENTRATION (NG/ML)		
DIAGNOSIS	AQUEOUS	SERUM	PLASMA
Cataract	1.4	≤0.5	≤0.5
Cataract	1.3	≤0.5	≤0.5
Failed graft	1.2	≤0.5	≤0.5
Failed graft	1.1	1.35	1.0
Cataract	0.83	≤0.5	≤0.5
Cataract	0.75	≤0.5	≤0.5
Cataract	0.73	≤0.5	≤0.5
Cataract	0.70	0.81	≤0.5
Cataract	0.68	≤0.5	≤0.5
Cataract	0.64	≤0.5	≤0.5
Cataract	0.62	≤0.5	≤0.5
Cataract	0.62	≤0.5	≤0.5
Cataract	≤0.5	1.52	≤0.5
Cataract	≤0.5	≤0.5	≤0.5
Glaucoma	≤0.5	≤0.5	≤0.5

than the serum at P = .01. The average concentration of the aqueous samples with detectable levels is 0.88 ng/ml.

Ohashi and associates[4] did not detect epidermal growth factor in human aqueous using a radioimmunassay. Watanabe and associates[5] found no detectable epidermal growth factor in rat aqueous. Shinoda and associates[6] reported high levels of epidermal growth factor in mouse aqueous. Further studies are necessary to resolve these discrepancies.

The physiologic significance of epidermal growth factor at the levels detected in human aqueous remains undetermined. Aqueous concentrations in excess of serum suggest that epidermal growth factor is either locally produced or actively transported. In vitro studies with rabbit endothelium[2] have found maximal epidermal growth factor effects at 10 ng/ml and no effect at 1 ng/ml. Having detected and quantitated epidermal growth factor in human aqueous humor, future studies must focus on the role of this growth factor in corneal endothelial health, healing, and storage, as well as possible epidermal growth factor effects on other anterior segment structures such as the trabecular meshwork.

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Superficial Retinal Refractile Deposits in Juxtafoveal Telangiectasis

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Idiopathic juxtafoveal telangiectasis is a retinal vascular anomaly confined to the retinal capillaries in the juxtafoveal region.[1] Its cause is unknown. In some patients the ophthalmoscopic findings may be subtle, and the vascular abnormalities may be detected only by fluorescein angiography. Gass and Oyakawa[2] reported refractile yellow opacities near the inner retinal surface in patients with bilateral parafoveal telangiectasis. We treated a patient who had minimal retinal thickening and no hemorrhages or exudates, in whom the refractile deposits were the most obvious ophthalmoscopic finding.

A 54-year-old man who had slow deterioration of near vision for nine years was referred to our institution. Medical history was unremarkable. Uncorrected visual acuity was R.E.: 20/30 +2 and L.E.: 20/25 +2. Pinhole improved visual acuity in the left eye to 20/20 but did not improve visual acuity in the right eye. Amsler grid examination demonstrated metamorphopsia centrally in both eyes. Intraocular pressures were 20 mm Hg in each eye. Results of slit-lamp examination and pupillary reactions were normal. There was minimal retinal thickening, and vascular abnormalities were not detected on biomicroscopy. Minimal retinal pigment epithelial mottling was observed in both eyes. More than 20 tiny, refractile deposits were observed in the macular area in the right eye, mostly in the temporal area. They appeared to be located anterior to the inner limiting membrane. Similar preretinal deposits were found in the left macula (Fig. 1). Fluorescein angiography demonstrated perifoveal telangiectasis in both eyes with minimal leakage in the late frames (Fig. 2).

We also reviewed photographs of 17 patients with angiographically proven idiopathic juxta-

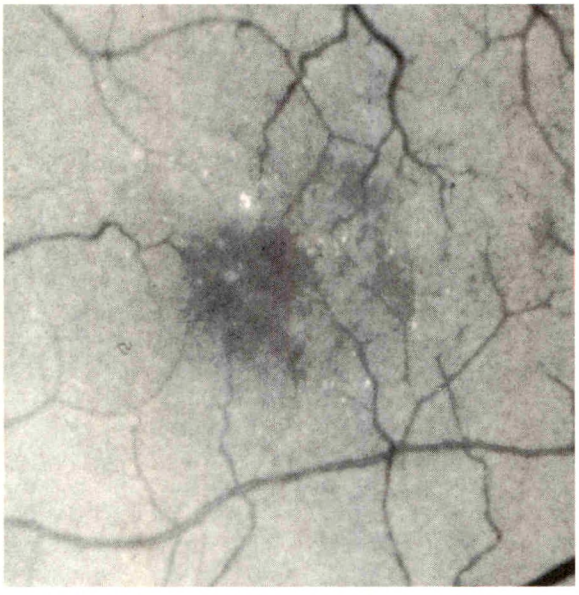

Fig. 1 (Moisseiev and associates). A magnified view of the left macula showing multiple deposits superficial to the retina.

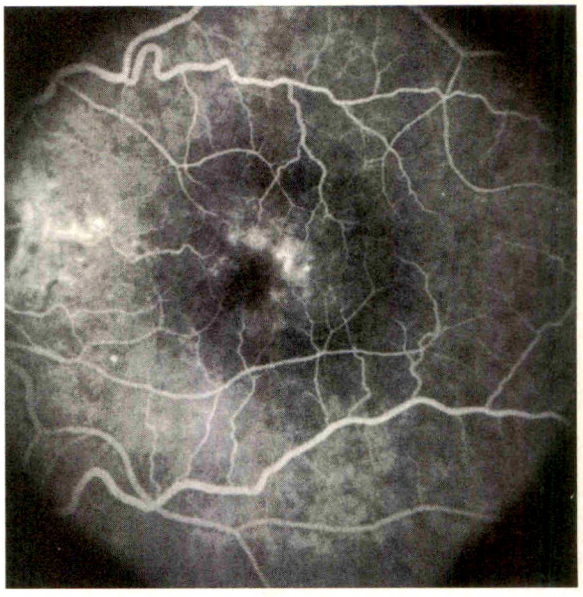

Fig. 2 (Moisseiev and associates). Left eye, Fluorescein angiography, late frame, showing leakage from telangiectasis 270 degrees around the fovea.

foveal telangiectasis treated at our institution between 1974 and 1988, and looked for superficial retinal and preretinal refractile yellow deposits in the juxtafoveal region. All 17 patients were white; nine were men and eight were women. Their age at the first examination ranged from 45 to 67 years (mean, 56 years). Refractile deposits were found in eight cases (47%), both in males (four cases) and in females (four cases). The deposits were found in one eye only in some patients with bilateral telangiectasis. The deposits were well defined, small (barely visible to about 40 μm in longest diameter), slightly irregular, gold, and refractile. They were located in the superficial layers of the retina, near the internal limiting membrane, or at the posterior hyaloid. The deposits could be distinguished from drusen and hard exudates by their superficial location, color, size, and shape. The number of refractile deposits ranged from one to more than 20, and they were located either overlying or adjacent to the telangiectasis. The deposits were superficial to the edematous area when there was macular thickening. There was no correlation between the number of deposits and the severity of the disease or other ophthalmoscopic signs.

We do not know the nature of the deposits, nor why they appear only in certain cases. They might be cholesterol or calcium deposits that either formed in the superficial retina or migrated to the posterior hyaloid. The deposits are more glistening and discrete than hard exudates. Our retrospective review indicates that they may be a common finding in patients with idiopathic juxtafoveal telangiectasis. When telangiectatic vessels are seen on fundus examination, especially with hemorrhages, hard exudates, or macular thickening, the diagnosis of retinal telangiectasis is obvious. It is the symptomatic patient (blurred vision, metamorphopsia), such as the patient described, without the above mentioned ophthalmoscopic findings, who poses the diagnostic challenge. A careful search for the superficial refractile deposits is a useful component of a thorough examination of the retina, especially when idiopathic juxtafoveal telangiectasis is suspected.

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Low-Dose Intraocular Tissue Plasminogen Activator for Treatment of Postvitrectomy Fibrin Formation

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Recombinant human tissue plasminogen activator injected intraocularly at a dose of 25 μg is an effective treatment for postvitrectomy fibrin formation.[1] Animal experiments, however, suggest that lower doses may also be effective.[2] The major potential complication of intraocular tissue plasminogen activator is hemorrhage.[1,3] Additionally, while animal experiments suggest that 25 μg of tissue plasminogen activator is not toxic to the retina,[2] a recent study demonstrated toxicity at 50- to 100-μg dosages.[4] This suggests that the therapeutic index at the 25-μg dose is low, particularly in air-filled or silicone oil-filled eyes that have limited intraocular fluid volume available for dilution of the tissue plasminogen activator. Since minimizing the dose of tissue plasminogen activator may improve the therapeutic index, we have used lower doses of intraocular tissue plasminogen activator than previously reported for the treatment of postvitrectomy fibrin.

We treated 17 eyes with complete fibrin pupillary membranes after vitrectomy with tissue plasminogen activator doses ranging from 12.5 μg to 3 μg (12.5 μg in nine eyes, 6 μg in six eyes, 3 μg in two eyes). Indications for vitrectomy were diabetic traction retinal detachment (four eyes), proliferative vitreoretinopathy (eight eyes), endophthalmitis after a penetrating injury with a retained intraocular foreign body (one eye), penetrating injury (two eyes), ruptured globe (one eye), and traction retinal detachment secondary to uveitis (one eye). Injections were given 24 hours (one eye), 48 to 72 hours (14 eyes), eight days (one eye), and 15 days (one eye) after vitrectomy.

Tissue plasminogen activator was prepared for intraocular injection by dissolving lyophilized tissue plasminogen activator (Genentech, San Francisco, California) in sterile water to an initial concentration of 100 μg/100 μl. This solution was then diluted in sterile balanced saline solution (Alcon Laboratories, Fort Worth, Texas) to a concentration of 25 μg/100 μl,[5] or in sterile physiologic saline to a concentration of 6 μg/100 μl. To administer 12.5 μg or 6 μg of tissue plasminogen activator, a volume of 50 μl or 25 μl of the 25 μg/100 μl solution was injected. Injections were given from a tuberculin syringe through a 30-gauge needle through the corneoscleral limbus (15 eyes) or pars plana (two eyes).

All of the eyes treated have shown complete resolution of the fibrin pupillary membrane within two hours of a single injection. Four eyes reaccumulated fibrin, a phenomenon also noted at the 25-μg dose[1]; three of these had received 12.5 μg and one had received 6 μg of tissue plasminogen activator. There have been no bleeding complications in these 17 eyes after administration of tissue plasminogen activator. Eight eyes underwent repeat fluid-gas exchange after tissue plasminogen activator injection.

It appears that intraocular tissue plasminogen activator is effective in clearing postvitrectomy fibrin at doses substantially lower than previously reported. Use of these lower doses may minimize the risks of intraocular hemorrhage and retinal toxicity. Further clinical experience with low-dose tissue plasminogen activator will better define the risk-benefit ratio associated with intraocular tissue plasminogen activator.

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Varix of the Vortex Ampulla Simulating a Choroidal Melanoma

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A variety of fundus lesions have been reported that simulate a choroidal melanoma.[1] I examined a patient in whom a varix of the vortex ampulla was the simulating lesion.

A 31-year-old man was referred to my institution for a malignant melanoma of the choroid. During an ocular examination a dark red-brown area of choroidal thickening measuring 2 × 3 disk diameters was discovered near the equator in the middle of the superonasal quadrant of the emmetropic right eye (Fig. 1). The choroidal thickening was not affected by changes in the position of the patient or of the globe. It disappeared promptly, however, with application of digital pressure to the eye (Fig. 2). The pressure exerted during contact ultrasonography was also sufficient to collapse the thickened area, making it impossible to demonstrate it with this examination technique. The choroidal thickening's equatorial location in the middle of the quadrant, continuity with the choroidal vortex system, and prompt disappearance with an increase in intraocular pressure supported the diagnosis of a varix of the vortex ampulla.

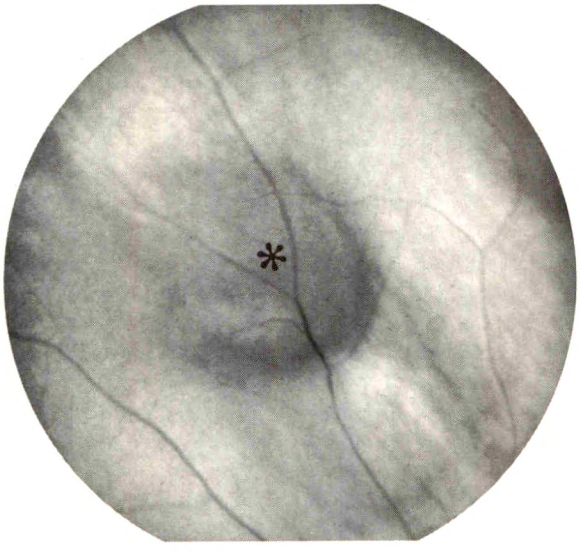

Fig. 1 (Buettner). Smoothly elevated and moderately pigmented choroidal lesion measuring 2 × 3 disk diameters in the middle of the superonasal quadrant of the left eye and retinal vessel bifurcation over center of lesion (asterisk).

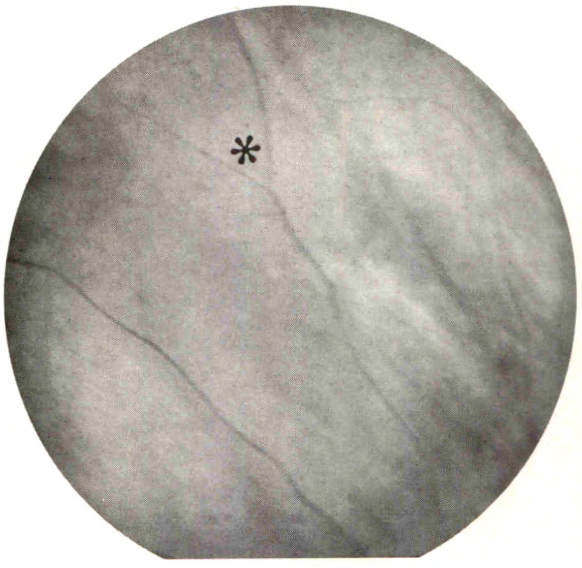

Fig. 2 (Buettner). The same area shown while digital pressure is applied to the globe. The choroidal lesion has disappeared. Asterisk identifies the same retinal vessel bifurcation marked in Figure 1.

The choroidal veins join in a vortical pattern in the middle of the oblique quadrants, forming an ampulla that measures about 5 mm in length and 2 mm in width. The ampulla narrows abruptly approximately 3 mm behind the equator, before it enters the emissary scleral canal and becomes the vortex vein that drains choroidal blood into the superior or inferior orbital veins.[2] Large vortex ampullae have a tendency to bulge, a phenomenon readily reversed by an increase in intraocular pressure.[3] An abnormally large ampulla, a varix, may cause marked choroidal thickening, which simulates a solid choroidal lesion. It can be engorged by lowering the patient's head or by a Valsalva maneuver,[4] or it may be prominently visible at all times without these maneuvers. Gaze-evoked kinking of the extrascleral portion of the vortex vein or gaze-evoked narrowing of the emissary

scleral canal have been reported as cause for intermittent enlargement of a varix.[4] In this patient, the emissary scleral canal was probably too narrow to allow normal venous drainage.

The choroidal elevation caused by a varix of the vortex ampulla can easily be differentiated from a choroidal melanoma by its continuity with the vortex system and its collapse with increased intraocular pressure.

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Persistent Hyperplastic Primary Vitreous Associated With Protein C Deficiency

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Protein C deficiency is an autosomal recessive disorder which is usually not compatible with long-term survival when in the homozygous state. Death usually results from recurrent venous thrombosis in the neonatal period.[1] Protein C is a vitamin K dependent plasma protein that is a potent inhibitor of the clotting cascade. It is activated by thrombin and acts as an anticoagulant by inactivating factors V and VIII.[2]

A 2,470-g, full-term girl was born to a 17-year-old gravida 1, para 1 girl. There was no known consanguinity. Shortly after birth, the infant was noted to have a shrill, high-pitched cry, purpuric areas on the feet, and enlarged cranial diameter. Computed tomography showed hydrocephalus involving the lateral ventricles with little remaining cortical mantle. Cultures of the blood, cerebrospinal fluid, urine, and sputum were negative. Prothrombin time, partial thromboplastin time, white blood cell count, hemoglobin level, hematocrit level, and platelet level were normal. Protein C antigen was less than 3%. The mother, father, and three of seven other family members tested had protein C antigen levels of less than 50% (normal, > 65%).

At 11 days of age, bilateral leukocoria was noted in the infant. An examination under anesthesia was performed at 12 days of age and showed corneal diameters of 10 mm in both eyes. Intraocular pressures by applanation were 16 mm Hg in each eye. The anterior chambers were nonexistent. The irides were bowed forward by the vascularized lens and vascularized retrolental masses. Real time B-scan echography showed a dense, funnel-shaped mass located anteriorly behind the lens with fibers extending from the apex of the funnel to the optic nerve. Standardized A-scan examination showed bilateral, highly reflective, irregularly structured, solid, immobile, avascular masses in the optic axis (Figure). The clinical and echographic diagnosis was bilateral persistent hyperplastic primary vitreous.

A pars plana vitrectomy and lensectomy were performed on the left eye when the patient was 17 days of age. During the operation, a dense retrolental mass was encountered. This mass of tissue was composed of fibrous material that surrounded the posterior surface of the lens and extended back to the surface of the optic nerve. The tips of many of the ciliary processes were elongated and incorporated into the central mass. The optical axis was cleared with the vitrectomy cutter. The retina, retinal vessels, and optic nerve appeared to be normal. The optic axis remained open during the immediate postoperative period. Because of the profound brain damage, the family deferred any further surgical intervention. Both of the infant's eyes are microphthalmic. After three years there appears to be light perception in the left eye, because she withdraws when exposed to bright sunlight.

There are two reports of dense retrolental masses in homozygous protein C deficiency associated with vitreous hemorrhage and retinal detachment.[1,3] It seems likely that both of

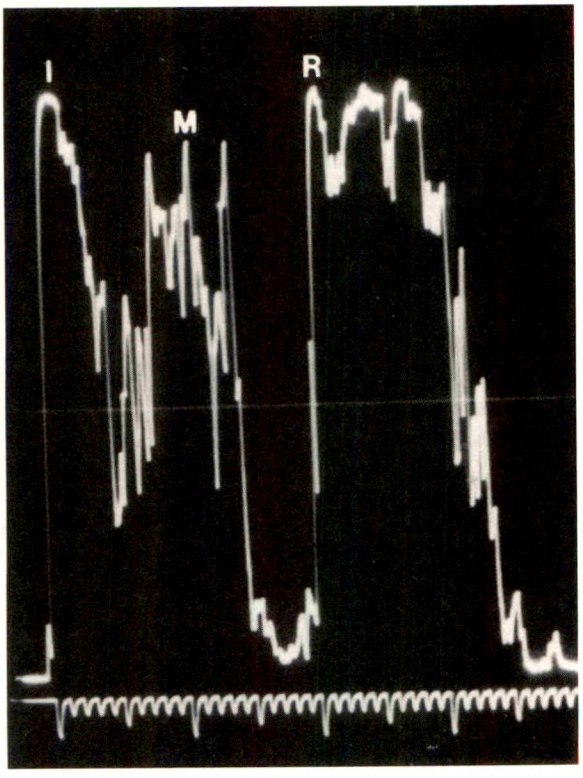

Figure (Hermsen and associates). Standardized A-scan echogram with initial spike (I), the ultrasound beam directed across the globe striking the highly reflective tissue mass of persistent hyperplastic primary vitreous (M) and the retina (R). In this view the mass appears to be somewhat regular but most of the lesion had an irregular internal structure.

these cases could have also represented instances of bilateral anterior persistent hyperplastic primary vitreous. The first patient, however, was not examined surgically, and postmortem examination was refused in the second patient. Bilateral persistent hyperplastic primary vitreous is uncommon, occurring in 11% to 12% of cases.[4,5] There is a high incidence of associated ocular and systemic abnormalities in cases of bilateral persistent hyperplastic primary vitreous.[5] We believe that this may occur with increased frequency in patients with homozygous protein C deficiency.

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Propionibacterium acnes Endophthalmitis Two Years After Extracapsular Cataract Extraction

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An 80-year-old woman underwent an uncomplicated extracapsular cataract extraction with placement of a posterior chamber intraocular lens in her right eye. Postoperatively she did well except for mild ocular irritation and occasional visual blurring. These symptoms were attributed to a low-grade anterior segment inflammation manifested by mild cell and flare. She was treated intermittently with topical cycloplegics and a mild antibiotic corticosteroid preparation containing tobramycin and dexamethasone. Visual acuity remained at R.E.: 20/40 for 24 months.

Twenty-four months after the operation, a routine examination disclosed visual acuity of R.E.: 20/30. Three weeks later, the patient developed intense pain, a marked decrease in vision, and loss of color perception in the right eye while on a regimen of topical medication. When we examined the patient, visual acuity was R.E.: hand motions; she had severe cells and flare, a 2-mm hypopyon, and no red reflex. She was referred for treatment of endophthalmitis. A preoperative examination several hours later showed visual acuity had decreased to R.E.: light perception only. A thick, white sheet of fibrin and inflammatory debris covered

the entire iris, obscuring the pupil and all iris details, and the aqueous humor was filled with cellular debris.

A dense, fluffy, 1-mm thick membrane was surgically peeled from the iris surface. The anterior segment was irrigated to remove residual debris and a pars plana vitrectomy was performed, removing both the vitreous and the peripheral lenticular material. Intraocular lens removal was not required. After completion of the vitrectomy, 0.05 mg of gentamicin sulfate and 0.5 mg of cefazolin were injected into both the anterior chamber and the vitreous cavity.

A culture of the dense fibrin membrane grew *Propionibacterium acnes*. Vitreous and aqueous specimens obtained at the beginning, during, and at the end of surgery showed no growth. The bacterium was sensitive to cefazolin, ceftriaxone, and gentamicin, but was resistant to tobramycin. The patient was given a regimen of intravenous cefazolin, topical fortified tobramycin (14 mg/ml), and cefazolin (50 mg/ml), every other hour for seven days. She was discharged with the same medications to be used four times daily and also 1% atropine twice daily.

Over the next three months, visual acuity improved to R.E.: 20/60. The anterior segment cleared on topical gentamicin sulfate and 1% prednisolone acetate each used twice daily. All medications were discontinued except for prednisolone acetate 0.1% twice daily. Twelve months after the vitrectomy visual acuity remained R.E.: 20/60, the anterior segment was clear, and the fundus was normal.

Indolent infections caused by *P. acnes* have been reported by Meisler and Mandelbaum.[1] Roussel, Culbertson, and Jaffe[2] reported a case of *P. acnes* infection occurring 16 months after surgery. The cause may be contamination during surgery, with the bacteria lodging in the peripheral lens capsule or cortical remnants. A low-grade, chronic inflammation developing a few weeks to several months after the initial surgery is characteristic in clinical endophthalmitis.

Our case underscores the need for suspicion when examining any eye with iritis or uveitis occurring even two years after extracapsular cataract removal. Topical corticosteroids used for the iritis may mask the underlying infection. Anterior chamber and vitreous taps may be negative despite the presence of bacterial endophthalmitis because cortical lens fragments or peripheral lens capsule can harbor the organism. In our patient, only the culture of a dense iris membrane was positive, while the aqueous and vitreous aspirate showed no growth. Treatment consists of appropriate antibiotics and removal of potentially infected lens remnants. *Propionibacterium acnes* is often resistant to aminoglycosides such as gentamicin sulfate, and is more likely susceptible to penicillin, clindamycin, chloramphenicol, and second and third generation cephalosporins.[1,3]

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Topical Cyclosporine Therapy for Ulcerative Keratitis Associated With Rheumatoid Arthritis

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Ulcerative keratitis in a patient with advanced rheumatoid arthritis can be difficult to treat. Microvasculitis and antigen/antibody complex deposition initiates lymphocytic phagocytosis and complement activation within the marginal and stromal portions of the cornea. Furthermore, keratoconjunctivitis sicca is associated with diffuse mononuclear cell infiltration of the lacrimal gland. Animal models of keratoconjunctivitis sicca implicate a suppressor/cytotoxic T-cell mediated disorder.[1] Topically applied cyclosporine, a specific T-cell immunosuppressant, has increased lacrimation,

decreased mucopurulent conjunctivitis of keratoconjunctivitis sicca, and reversed corneal infiltration in both animals and humans.[1] Topical cyclosporine has also reduced or prevented immunograft reactions in corneal transplant tissue,[2] and oral cyclosporine has been effective in refractory scleritis.[3]

Zierhut and associates[4] reported results of 2% topical cyclosporine therapy in two patients with advanced rheumatoid arthritis who had nonhealing marginal corneal ulcers. In one patient, topical cyclosporine closed and healed a corneal perforation on two occasions. Epithelialization of these ulcers required two or three times daily dosages for four to nine days of therapy. We used topical cyclosporine to arrest corneal graft melting that was refractory to other therapies.

A 66-year-old woman had advanced rheumatoid arthritis for over 20 years. Having developed Sjögren's syndrome, she had progressive deterioration of the ocular surface. Keratoconjunctivitis sicca and bilateral central corneal melting did not reverse with vigorous ophthalmic lubrication, tarsorrhaphy, oral corticosteroids, and systemic immunosuppression (methotrexate, 7.5 mg/week). Visual acuity worsened to light perception and projection in each eye as corneal ulcers were nonhealing and continued to melt centrally. Lamellar keratoplasty was ineffective in the left eye. The patient's corneas thinned to Descemet's layer with impending perforation that warranted bilateral penetrating keratoplasty. Postoperatively, the right corneal graft began melting and developed marginal and central stromal infiltration and ulcerative changes (Fig. 1). The methotrexate was increased to 10 mg per week without improvement. We began 2% topical cyclosporine solution four times daily in the right eye after repairing a wound dehiscence resulting from a suture cutting into the melting graft (Fig. 1). Over the next four weeks, the nearly perforated right donor graft healed and reepithelialized (Fig. 2). Cyclosporine was later used in the left eye with quick resolution of the ulcerated graft and improvement of corneal clarity. The patient is taking 2% cyclosporine solution twice daily in both eyes. Uncorrected visual acuity has improved to 20/400 in each eye, and the graft is stable.

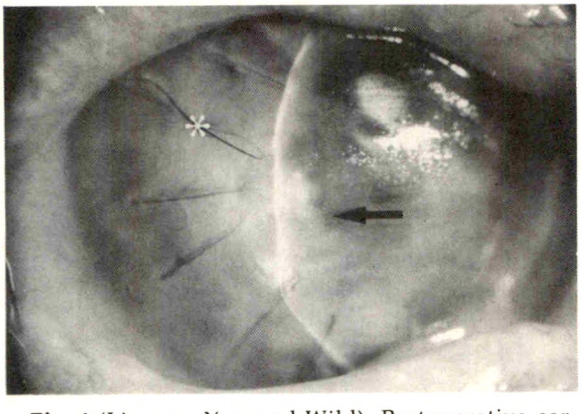

Fig. 1 (Liegner, Yee, and Wild). Postoperative corneal graft appearance with the 10 o'clock suture cutting into the graft (asterisk), central corneal ulceration, and thinning (arrow) diffuse stromal infiltration of the entire graft.

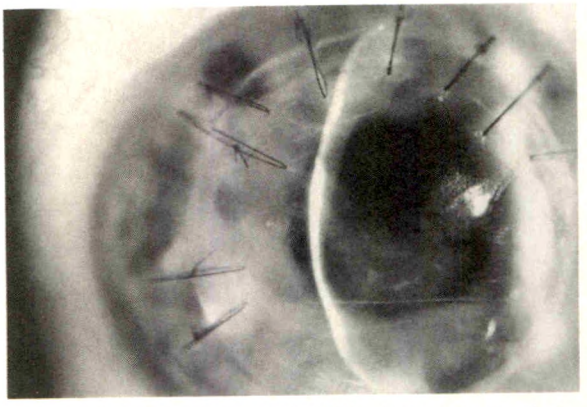

Fig. 2 (Liegner, Yee, and Wild). Appearance of the corneal graft after treatment with 2% cyclosporine. Note the improvement of the ocular surface and iris details and the significant resolution of corneal ulceration and infiltration.

Ocular manifestations in rheumatoid arthritis can indicate a poor prognosis. These include necrotizing scleritis, ocular vasculitis, and peripheral and central ulcerative keratitis potentially causing corneal perforation. The rapid and encouraging results with topical cyclosporine in our patient closely mirror those of similar reported cases.[4] Cyclosporine's effect on T-cell activation and subsequent suppression of chemotactic factors with reduced activation of proteases may partially explain its beneficial effect. Improved tear production also benefits the keratoconjunctivitis sicca and contributes to corneal healing.

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Acute Infantile Leukocoria

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The differential diagnosis of leukocoria in the pediatric age group includes cataract, which may be an isolated condition or an accompanying part of a whole syndrome. Acute leukocoria is a rare condition that is usually in relation to a traumatic event.

Posterior lenticonus, which is generally unilateral, progressively leads to cataract formation over a period of years.[1] This has been reported to occur bilaterally in the mode of autosomal recessive or dominant transmission.[2]

We treated a child who had acute leukocoria with bilateral posterior lenticonus. The child's father underwent cataract surgery at the age of 30 years for bilateral lens opacities, secondary to posterior lenticonus.

At the age of 2 years, the boy was first examined at our clinic for a strabismus and visual acuity less than 20/160 on picture cards visual assessment.. On examination the ocular movements were full. The cover test showed a right phoria to tropia, with a poorer fixation in the right eye. The corneas were clear, the anterior chamber was deep, and the pupils were round and symmetrically reacting to light. Examination with the slit lamp showed a mild lenticonus in both eyes with posterior subcapsular cataracts, more progressed in the right eye. The fundi were well visualized and normal. A myopia of −7.0 diopters was measured in both eyes by retinoscopy with 0.5% cyclopentolate hydrochloride. The child was fitted with spectacles.

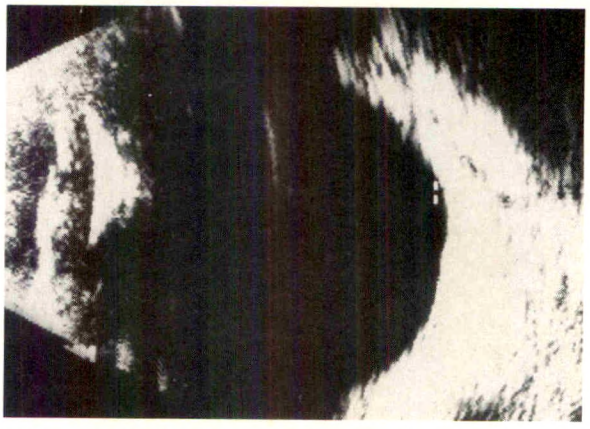

Fig. 1 (de Courten and Faggioni). B ultrasonographic scan of the right eye, with intumescent cataract demonstrating the posterior lenticonus.

At the age of 5 years, follow-up examination disclosed a slight increase in the lenticular opacities, and best-corrected visual acuity was 20/60 in each eye. A few weeks after this visit, the mother noticed that the boy had a white pupil in the right eye. There was no history of trauma. On examination, visual acuity in the right eye was reduced to light perception because of an intumescent cataract. B-scan echography demonstrated a markedly increased bulging of the posterior lenticonus (Fig. 1).

Removal of the right intumescent cataract was performed under general anesthesia. Surgery was complicated by vitreous mixed with lens material. The rupture of the posterior capsule and the bulging were evident as soon as the anterior capsule was opened. Anterior vitrectomy was performed with thorough cleaning of the lens and capsular material. The child was fitted with a contact lens postoperatively. Nevertheless, one year later, he underwent a second operation on the right eye because of contact lens intolerance, with the fixation of a sulcus implanted lens.

Because of the complicated course in the right eye and the progression of lens opacities in the left eye, we extracted the lens in the left eye three months later (Fig. 2). At that time we noticed a sharply delimited circle in the posterior capsule, bulging posteriorly. The lens material was easily removed by an aspiration-irrigation system, the posterior capsule was kept intact, and a posterior chamber polymethyl-

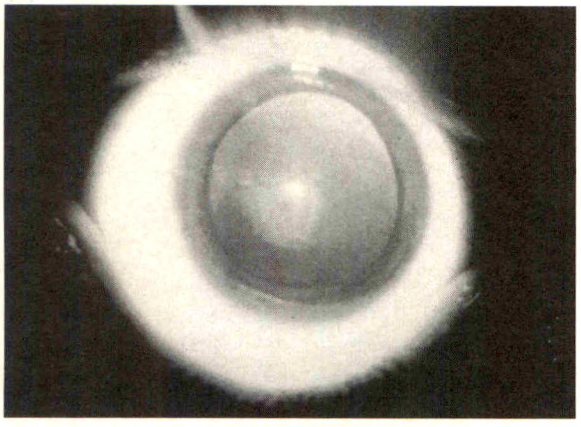

Fig. 2 (de Courten and Faggioni). Posterior cataract on the left eye immediately before extracapsular cataract extraction and posterior lens insertion.

methacrylate lens was inserted. Best-corrected visual acuity remained 20/25 in each eye. Six months after this final operation, the eyes remained quiet, and the intraocular lenses were well tolerated. Acute leukocoria, which developed in this child's right eye without any trauma, was probably caused by the rupture of the posterior capsule of its posterior lenticonus.

Francheschetti and Rickeli[3] and Kahlil and Saheb[4] reported that the subcapsular epithelium overlying the lenticonus is hyperplastic and weak. We believe that in our patient the possible mechanism for this acute leukocoria is progressive weakening of the posterior capsule eventually resulting in rupture. Direct contact between the lens material and the vitreous occurred, and rapid lens opacification ensued. Acute leukocoria in a child with posterior lenticonus might be the consequence of spontaneous rupture of the lenticular capsule.

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Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Fluorouracil Filtering Surgery Study One-Year Follow-up

EDITOR:

In the article, "Fluorouracil filtering surgery study one-year follow-up" by The Fluorouracil Filtering Surgery Study Group (Am. J. Ophthalmol. 108:625, December 1989), the authors recommend the use of subconjunctivally injected 5-fluorouracil after filtering surgery in eyes with uncontrollable glaucoma after cataract extraction and in phakic eyes after failed filtering surgery, despite the early postoperative adverse effects of epithelial toxicity. This conclusion warrants further comment.

In this study, aphakic and pseudophakic eyes were placed in the same broad group. Therefore, eyes with vitreous filling the anterior chamber and broadly scarred incision sites were considered comparable to those with well-positioned posterior chamber intraocular lens implants and intact posterior capsules after phacoemulsification. Statistical significance is achieved mainly through the great difference between postcataract extraction groups. It would be of great interest if the authors could further analyze these data with respect to the type of cataract surgery previously performed, the status of the vitreous face, and the need for anterior vitrectomy during the glaucoma surgery. Gross[1] reported that the success of glaucoma filtering surgery in pseudophakic eyes with posterior chamber lenses approaches that in phakic eyes.

In Figure 2, mean intraocular pressure in eyes treated with 5-fluorouracil was significantly lower than that of control eyes throughout postoperative days 7 through 14. At the same time, however, wound leaks were more frequently seen in treated eyes as compared to

control eyes. The authors do not state if patients with wound leaks were included in these data, therefore artifactually decreasing the mean intraocular pressure. More control eyes required digital massage during this time. Did the recorded intraocular pressure represent the premassage, postmassage, or mean value?

Among control eyes, 22 (20%) had wound leaks, 88 (81%) had punctate epitheliopathy, and 18 (17%) had persistent epithelial defects. The incidence of these postoperative complications appears to be much greater than that previously reported. For example, Spaeth reports a 5% incidence of postfiltering wound leaks.[2] The authors do not comment as to the causes of these disparities (for example, because of study population, presence of scarred conjunctiva, or pre-existing corneal disease). Seven patients treated with 5-fluorouracil developed bleb rupture, but it is unclear as to the type of further treatment these patients required.

Gressel, Parrish, and Heuer,[3] reported that the incidence of suprachoroidal hemorrhage is higher with the use of 5-fluorouracil, yet an equal number of patients in each group developed this complication. How did the authors differentiate suprachoroidal hemorrhage from effusion, the latter occurring after glaucoma surgery in many eyes without adverse effects? Several eyes required reformation of a flat anterior chamber. How was this defined, for example, cornea-lens touch or iridocorneal touch? Several other procedures were performed but not described.

This study markedly expands the field of research in filtering surgery for glaucoma and may prevent blindness in these patients with complications. Since the authors qualify their success with reports of increased postoperative morbidity, it is only through further analysis of these results that ophthalmologists can isolate patients who may sustain greater benefit than that reported and those who may not.

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EDITOR:

We read with interest the report of The Fluorouracil Filtering Surgery Study Group (Am. J. Ophthalmol. 108:625, December 1989), on the use of 5-fluorouracil to improve the chances of success of trabeculectomy in eyes at high risk of failure. The authors report seven cases of bleb rupture in 104 eyes treated with 5-fluorouracil, compared to none in the control group.

We started using 5-fluorouracil in 1988 and have treated 35 eyes with a minimum follow-up of six months (range, six to 14 months). We used 50 mg of 5-fluorouracil, given as ten injections over a two-week period, a somewhat lower dosage than that reported in this series. Twelve eyes have developed cystic blebs, compared to eight eyes in a matched series undergoing identical surgery ($P = .2$). In the group treated with 5-fluorouracil, however, these cystic blebs have been associated with transconjunctival drainage and chronic hypotony in eight eyes, compared to only one eye in the control group ($P = .002$). Three eyes developed a sudden decrease in intraocular pressure associated with a Seidel-positive area of cystic degeneration of the bleb and shallowing of the anterior chamber at six, ten, and 12 weeks after the operation, respectively.

The authors should comment further on the patients with bleb rupture with regard to bleb structure, and the timing of this complication. We would also be interested to know if they are experiencing similar complications with thin avascular blebs, transconjunctival drainage, and hypotony.

WENDY FRANKS, M.D.
ROGER HITCHINGS, M.D.
London, England

Reply

EDITOR:

We appreciate Dr. Fourman's interest in the one-year results of The Fluorouracil Filtering Surgery Study Group.

The analysis of the aphakic and pseudophakic eyes will be reported in a later publication along with other subgroup analyses.

Throughout the study the intraocular pressures were recorded before ocular massage. The intraocular pressure data for the first two postoperative weeks included all eyes; however, when the eyes with wound leaks were omitted, the mean intraocular pressures on each postoperative day and the P values were virtually unchanged.

High incidences of wound leaks, punctate epitheliopathy, and epithelial defects were documented in the one-year follow-up, compared to previous reports. We suspect that the increased incidence of wound leaks was based on careful Seidel testing that we performed at least once daily during the first two postoperative weeks. We also included leaks through suture tracts, leaks through the conjunctival wounds, and any conjunctival buttonholes.

Eyes with bleb ruptures were a heterogeneous group. This category was devised to determine if excessively thin blebs were more likely to be associated with 5-fluorouracil treatment and as a result were more likely to rupture spontaneously. All bleb ruptures except one included the development of multiple pinhole-sized leaks usually during the first two postoperative weeks.

The incidence of suprachoroidal hemorrhages was not different in the two groups. The low incidence is probably because of the selection of trabeculectomy rather than a full-thickness filtration procedure. Profound postoperative hypotony is widely regarded as the precipitating event in the cascade of events that leads to a serous choroidal effusion, stretching of the long posterior ciliary vessels, and then a fracturing of these vessels as they exit through the sclera into the suprachoroidal space under increased intravascular pressure. Since all the patients in the study underwent guarded procedures, we believe they suffered choroidal hemorrhages less frequently because their early postoperative intraocular pressures tended to be higher than if they had undergone full-thickness procedures.

The discrimination between a choroidal effusion and a suprachoroidal hemorrhage was made on a clinical basis. Our experience has been that suprachoroidal hemorrhages are usually associated with profound orbital pain. Thus, the clinical history, as well as transillumination or echography, was helpful in differentiating choroidal effusions from suprachoroidal hemorrhages. The course of suprachoroidal hemorrhage after filtering surgery is also much different from choroidal effusion.

Patients in the 5-fluorouracil group were more likely to undergo anterior chamber reformation for cornea-lens touch or impending touch than those in the standard treatment group, presumably related to the increased incidence of wound leaks and hypotony.

The other procedures performed referred to those procedures for which more than topical anesthetic was used. In the 5-fluorouracil group, five patients underwent the following additional procedures: one intracapsular cataract extraction and anterior vitrectomy for malignant glaucoma; one penetrating keratoplasty and intraocular lens exchange; one surgical excision of conjunctival cyst; one retinal detachment repair with combined pars plana vitrectomy; and one pars plana vitrectomy with cryopexy. In the standard treatment group, three patients underwent the following additional procedures: one vitreous biopsy for suspected endophthalmitis; one anterior vitrectomy; and one vitrectomy with cryopexy and implantation of a Stage 1 Molteno drainage device.

We share the concern of Drs. Franks and Hitchings that thin, multicystic blebs with transconjunctival flow may be more likely to rupture and develop late postoperative infections. The category of bleb rupture was devised to determine if excessively thin blebs were more likely to be associated with 5-fluorouracil treatment and, as a result, were more likely to rupture spontaneously. Six of the seven eyes with bleb ruptures developed pinpoint areas of leakage over the bleb within the first seven postoperative days. We believe that the categorization of transconjunctival leakage over the bleb as bleb rupture was misleading and probably more accurately reflects the direct toxic result of 5-fluorouracil on conjunctival epithelial cell proliferation. In only one patient was a bleb rupture observed at the three-month follow-up. The investigator described this as a "pinpoint leak in area of cystic intrapalpebral bleb." Continued follow-up will define the course of these filtering blebs. We apologize for the misleading report of transconjunctival leaks in the initial postoperative period as bleb ruptures.

Within the next year we hope to publish additional analyses of the study population to provide additional information regarding the patient characteristics that might help distin-

guish the patients who will benefit from postoperative subconjunctival 5-fluorouracil from those who are more likely to suffer complications. We cannot, however, overemphasize that the results reported simply reflect the clinical course of patients during the first year. It is too early to draw conclusions regarding either the long-term safety or efficacy of 5-fluorouracil as an adjunct to filtering surgery. This underscores the need for the vigilant follow-up of all patients in the study.

THE FLUOROURACIL FILTERING
SURGERY STUDY GROUP
Miami, Florida

Cyanoacrylate Tissue Adhesive in the Management of Recurrent Retinal Detachment Caused by Macular Hole

EDITOR:

The article, "Cyanoacrylate tissue adhesive in the management of recurrent retinal detachment caused by macular hole," by S. M. Sheta, T. Hida, and B. W. McCuen (Am. J. Ophthalmol. 109:28, January 1990), describes a valuable new tool for the vitreoretinal surgeon to manage failed retinal detachments with macular holes. In the discussion, the authors review previous surgical options for the management of failed retinal detachment with macular hole, including pneumatic retinopexy, vitrectomy with fluid-air exchange, and macular coagulation or buckling. We reported a technique of using radial retinotomy around the edges of a macular hole to treat failed retinal detachments with epiretinal membranes.[1] This technique should be considered as an additional surgical option in the management of retinal detachment with macular hole, especially in patients with proliferative vitreoretinopathy in the posterior pole. In selected patients, the use of radial retinotomy in the macula might obviate the need for cyanoacrylate retinopexy.

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DANIEL F. MARCUS, M.D.
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Reference

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Reply

EDITOR:

We thank Dr. Bovino and Dr. Marcus for pointing out their technique of radial retinotomy in the macula as an additional method of dealing with recurrent retinal detachment secondary to macular holes. They reported success with this technique in the only patient who would fit our criteria for inclusion. We reemphasize that we used cyanoacrylate retinopexy in our patients to avoid techniques with potentially higher risks and complications. We would consider a technique in which retinal cuts are made in the center of the fovea to be potentially more risky than simply closing the retinal break without enlarging it.

SHERIF M. SHETA, M.D.
Cairo, Egypt
TETSUO HIDA, M.D.
Tokyo, Japan
BROOKS W. MCCUEN II, M.D.
Durham, North Carolina

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Microsurgery of Retinal Detachment. By Mireille Bonnet. New York, Field & Wood Medical Publishers Inc., 1989. 313 pages, index, illustrated. $120

Reviewed by CHRISTOPHER F. BLODI
Iowa City, Iowa

A generation of retinal surgeons has learned to rely on the indirect ophthalmoscope as the linchpin of retinal reattachment surgery. Dr. Bonnet uses a microscope and a fundus contact lens to identify and to treat retinal abnormalities, to suture scleral implants, and to drain subretinal fluid. She believes her techniques lessen intraoperative complications, lower the rate of postoperative cystoid macular edema, and lower the failure rate for easy detachments.

The first half of this greatly enlarged second edition is intended to help clarify the decision-making steps needed to select the most appropriate surgical procedure. The discussion of preoperative examination techniques and intraoperative maneuvers has been expanded. The drawings and photographs are useful. Unfortunately, the author does not fully discuss her approach to the common problems of media opacity and small pupils. I believe it is the indirect ophthalmoscope that gets me through these difficult situations when I would hate to have to depend on a contact lens examination. The discussion of treatment for fellow eyes and anesthesia preference is extremely limited.

The second half of the book includes a discussion of approaches to different types of retinal detachments. The author's bias against subretinal fluid drainage extends to chronic detachments and even cases with proliferative vitreoretinopathy. A more complete discussion of conventional vitrectomy techniques is included in this edition. Many surgeons will disagree with the unusual sequential gas-fluid exchange procedure described, which eschews air pumps and simultaneous fluid removal with gas infusion. The use of lyophilized human tissue for scleral buckling will likewise seem unusual to recently trained surgeons. The text will be of interest to the experienced retinal surgeon, who will learn that there are different ways of performing successful retinal reattachment surgery.

Books Received

Malformaciones Oculares. Oftalmologia en Bolivia. Enfoque Geografico y Antropologico, vol. 1. By Teodoro Aracena Ibarra. Cochabamba, Bolivia, Editorial Serrano Ltda., 1989. Softcover, 255 pages, illustrated.

This is a well-illustrated review of ocular malformations. There are 313 figures, of which 72 are in color.

Providing Services for People With Vision Loss. A Multidisciplinary Perspective. Edited by Susan L. Greenblatt. Lexington, Massachusetts, Resources for Rehabilitation, 1989. Softcover, 136 pages, illustrated. $19.95

Every patient with irremediable visual loss spends some time with an ophthalmologist. The ophthalmologist who has spent an evening with this book will be better equipped to talk to the patient who is going blind.

Sudden Vision. The "RK" Procedure for Nearsightedness and Other Wonders of Modern Ophthalmology. By John Crater. Thorofare, Slack Inc., 1990. Softcover, 213 pages, index, illustrated. $15

This book is about radial keratotomy written by a patient for other patients who might be curious about the procedure. It is done in a comic style with cartoons on every page. The author tries to make his points "as forcefully as

he can without making a nuisance of himself." The reader who believes that this goal has been attained will find the pages packed with good information.

The Book List

Cataract Surgery. Before and After. Cataracts and Their Cure. By Robert I. Johnson. Thorofare, Slack Inc., 1990. Softcover, 26 pages, illustrated. $100 per 25 copies

Cataract Surgery. Before and After. Having Cataract Surgery. By Robert I. Johnson. Thorofare, Slack Inc., 1990. Softcover, 34 pages, illustrated. $100 per 25 copies

Clinical Optics. Ophthalmic Technical Skills Series. By Budd Appleton. Thorofare, Slack Inc., 1990. Softcover, 84 pages, index, illustrated. $37

Clinical Practice of Glaucoma. By William C. Stewart. Thorofare, Slack Inc., 1990. 424 pages, index, illustrated. $90

Glare and Contrast Sensitivity for Clinicians. Edited by M. Princeton Nadler, David Miller, and Daniel J. Nadler. New York, Springer-Verlag, 1990. 150 pages, index, illustrated. $69

The Ocular Fundus. A Photographic Documentation Atlas With Diagnostic and Therapeutic Guidelines. By Horst Huismans. Baltimore, Williams & Wilkins, 1990. 215 pages, index, illustrated. $129.50

Ophthalmic Examination and Basic Skills. By Michelle Pett Herrin. Thorofare, Slack Inc., 1990. Softcover, 156 pages, index, illustrated. $37

Ophthalmic Lasers. A Second Generation. Edited by Wayne F. March. Thorofare, Slack Inc., 1990. 363 pages, index, illustrated. $90

Ophthalmology Clinics of North America, vol. 1. New Techniques in Glaucoma Surgery. Edited by Robert L. Stamper, Theodore Krupin, and Martin B. Wax. Philadelphia, W. B. Saunders Co., 1988. 280 pages, index, illustrated. $31

Ophthalmology Monographs 1. Retinal Detachment, ed. 5. By George F. Hilton, Edward B. McLean, and Elaine L. Chuang. San Francisco, American Academy of Ophthalmology, 1989. Softcover, 227 pages, index, illustrated. $35 (AAO members), $50 (nonmembers)

Opticianry, Ocularistry, and Ophthalmic Technology. By Basil Blair, Budd Appleton, Norma Garber, Mark Crowe, and Michael T. Alven. Thorofare, Slack Inc., 1990. Softcover, 137 pages, index, illustrated. $37

Obituary

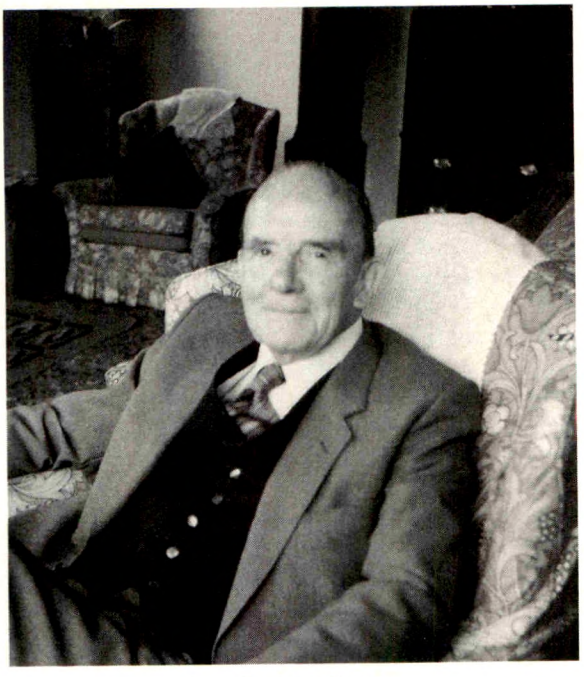
IAN COMYN FRASER
1902–1990

In 1902 Ian Comyn Fraser was born of Scottish parents at Inverness, Scotland; 87 years later he died, in Shrewsbury, England.

When he was 6 years of age, his family set sail, like many compatriots, for New Zealand. Ian grew up there, revelling in the unfettered colonial life. His lifelong enthusiasm for golf and bridge was kindled there. After Otago Boys' High School he graduated in medicine at Otago University in 1925. The two-year internship was succeeded along a route common amongst New Zealand medical men, travelling as ship's Surgeon to England. Postgraduate study included both ophthalmology at Moorfields Eye Hospital and otolaryngology. Edinburgh became important for him because it was there that he not only passed the Fellowship of the Royal College of Surgeons but met his wife to be, Margaret, sister of Dr. Grant Peterkin, who was later to become an eminent dermatologist.

After a brief but fruitless sojourn back in New Zealand he returned to England to marry and settle, his first Consultant post being in the Channel Island of Guernsey.

At the outbreak of World War II Ian and his wife and son were evacuated when Germany invaded the only part of the United Kingdom to be occupied. After enlisting in the Royal Army Medical Corps he experienced the blitzkreig in London and in 1942 was drafted to the Middle East. He rose in rank to Lt. Colonel and became advisor in ophthalmology, second in command



Ian Comyn Fraser
1902–1990

to Stewart Duke-Elder in the Iran-Iraq theatre centered on Baghdad.

In 1945, because of his wife's illness, he was returned to the United Kingdom where he became advisor to Scottish Command. After demobilization in 1945, an application was successful for his final Consultant post at the Eye, Ear and Throat Hospital in Shrewsbury, England.

His colleague was F. A. Anderson, then secretary of the Oxford Ophthalmological Congress, and in 1947 Ian succeeded him in that position. From this point his own commitment to this venerable institution (founded in 1909 by Robert Doyne) was complete. He had become a member in 1931. During his period as secretary and editor of the Transactions from 1947 until 1964 the Congress flourished. After the tragic and untimely death of his wife in 1957 he immersed himself in the affairs of the Congress and retained that passion till his death.

Ian established lasting association with many congressees from around the world. He was wont to reminisce about the American ophthalmologists among whom were numbered Derrick Vail and particularly your own Editor-in-Chief, Professor Frank Newell. His secretary and he went to endless trouble to ensure a warm welcome to the congressees and as much comfort as the essentially spartan Balliol College, Oxford, could furnish. His loyalty and service were crowned in 1965 and 1966 when he became the Congress's Master.

Apart from his hospital duties, Ian was eye surgeon to a number of schools for the blind in Shropshire. (These had been moved away from London at the outbreak of war and remained after the cessation.)

Ian was a wise, skillful surgeon, much loved by patients and colleagues. His devotion to ophthalmology was extended after his formal retirement in 1967 when he became advisor for the Royal College of Surgeons touring England and beyond. One trip was to his New Zealand homeland with Philip Jameson Evans, one of his closest friends. (The text of a lecture about the Oxford Ophthalmological Congress delivered at that time is now in press.)

After a succession of illnesses during the past five years, Ian died on 2 February 1990. He is survived by his son Keith, his daughter-in-law, and two grandchildren.

I. A. R. BROWN, F.R.C.S.

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

Aviation Space and Environmental Medicine

Touching the cornea enhances pharmacologic dilation of the pupil, mainly in the dark iris. Carlson, D. W., and Tychsen, L. (Depts. Ophthalmol., Anatomy and Neurobiol., Washington Univ. School of Med., Box 8096, 660 S. Euclid Ave., St. Louis, MO 63110). Aviat. Space Environ. Med. 60:994, 1989.

To test the impression that dark irides dilate better after touching the cornea phenylephrine and tropicamide were instilled in both eyes after touching one cornea. The diameter of the pupils were measured by means of a video infrared pupillometer. In white subjects the mean difference of pupil diameter at 30 minutes averaged 0.2 mm. In black subjects the mean difference of pupil diameter at 30 minutes averaged 1.3 mm. The statistical difference was significant ($P < .001$). This difference was also significant at 9, 12, and 24 minutes after instillation of the drops. The difference between the touched and the control eyes was not statistically different for the white subjects at any time interval. (2 figures, 4 references)—David Shoch

British Journal of Ophthalmology

Primary optic nerve sheath meningioma. Wright, J. E., McNab, A. A., and MacDonald, W. I. (Moorfields Eye Hosp., City Road, London EC1V 2PD, England). Br. J. Ophthalmol. 73:960, 1989.

In 50 patients diagnosed as having a primary optic nerve sheath meningioma followed for up to 15 years, 44 of the patients had histologic confirmation of the diagnosis and six had typical clinical and radiologic features. The tumor had an onset in 33 women at an average age of 43.2 years. In 17 men the average age of onset was 33.3 years. Intracranial extension was much more common in men whose symptoms began before the age of 20 years. This difference affected the management of these lesions. For tumors diagnosed after the age of 40 years no treatment is provided unless the tumor enlarges and produces disfiguring proptosis. Then either radiation or local excision is advised. Patients less than 40 years old should be treated more vigorously. The authors recommend optic nerve excision for all patients less than 30 years old as the chances of intracranial spread are considerable. The entire optic nerve from the chiasm to the globe should be excised by a transfrontal approach even when the vision is relatively good. (4 figures, 4 tables, 13 references)—David Shoch

Long-term follow-up of acute multifocal posterior placoid pigment epitheliopathy. Williams, D. F., and Mieler, W. F. (Dept. Ophthalmol., Med. College of Wisconsin, 8700 W. Wisconsin Ave., Milwaukee, WI 53226). Br. J. Ophthalmol. 73:985, 1989.

Eleven patients with acute multifocal posterior placoid pigment epitheliopathy were followed for 47 to 175 months (mean, 106). The final visual acuity was 20/30 or better in 17 of the 18 affected eyes. Seven of 18 affected eyes developed progressive mild alterations of the retinal pigment epithelium. In one eye the visual acuity decreased from 20/25 to 20/60. In this eye retinal pigment atrophy involved the fovea. (3 figures, 2 tables, 25 references)—David Shoch

Retinal dysfunction as an initial ophthalmic sign in AIDS. Brodie, S. E., and Friedman, A. H. (Dept. Ophthalmol., Box 1183, Mount Sinai Med. Ctr., 1 Gustave Levy Pl., New York, NY 10029). Br. J. Ophthalmol. 74:49, 1990.

Most retinopathies associated with AIDS have been caused by cytomegalic virus, herpes simplex virus, or toxoplasmosis. Three patients in this study had severe retinal dysfunction with visual loss and electroretinographic abnormalities that preceded the development of visible exudative or hemorrhagic lesions of the retina and pigment epithelium. In one patient visual loss was the initial symptom of AIDS. Vitreous aspiration disclosed only a few lymphocytes, histiocytes, and neutrophils. Cultures for bacteria, fungi, and viruses were negative. A second patient had a diffuse vitreous infiltrate in both eyes and one eye a single

whitish lesion about 0.5 disk diameter in size. Visual acuity was reduced to 20/200. The fellow eye was normal. The tests for opportunistic infections were negative and the patient's eyes remained unchanged until his death several months later from disseminated cytomegalic virus disease. The third patient showed no sign of any retinal or choroidal involvement but had lost vision in both eyes over an eight-week period. Vitreous haze was present bilaterally and the photopic and scotopic electroretinogram was substantially reduced in both eyes. The authors postulate that the absence of ophthalmoscopically visible lesions may support the thesis that these eyes had direct invasion by human immunodeficiency virus. (7 figures, 4 references)—David Shoch

British Medical Journal

Superglue inadvertently used as eyedrops. Lyons, C., Stevens, J., and Bloom, J. (Moorfields Eye Hosp., London EC1V 2PD, England). Br. Med. J. 300:328, 1990.

Six patients inadvertently instilled cyanoacrylate nail adhesive into their eyes. The bottles of adhesive were similar in shape and size to bottles of eyedrops and one of them even had a name that contained the prefix "ey." The authors suggest that eyedrops have standard colored caps and that distribution of nonpharmaceutical chemicals in plastic dropper or bottles should be banned. They further suggest labelling in braille on the underside of medication bottles to help partially sighted patients distinguish their medications. (1 table, 9 references)—David Shoch

Journal of the Royal Society of Medicine

Leber's optic neuropathy and mitral valve prolapse. Banerjee, A. K., Hykin, P. G., MacSweeney, J. E., and Sanders, M. D. (Westminister Hosp., London SW1, England). J. R. Soc. Med. 83:55, 1990.

In his original study Leber reported cardiovascular symptoms, usually palpitations. A 44-year-old man had electrocardiographic abnormalities. Echocardiography demonstrated a mitral valve prolapse that was confirmed on cardiac angiography. Two years later he developed optic neuropathy with decreased vision and dilated capillaries on both disks. His mother had bilateral optic atrophy and a nephew was diagnosed as having Leber's optic neuropathy. The authors recommend that patients with Leber's optic neuropathy and their asymptomatic relatives undergo echocardiography as well as electrocardiography. (1 figure, 6 references)—David Shoch

Morbidity and Mortality Weekly Report

Pneumococcal endophthalmitis after ocular surgery—Alaska, California. Jones, M., and Middaugh, J. Morbid. Mortal. Weekly Rep. 39:71, 1990

Two patients in Alaska and two in California developed endophthalmitis after corneal transplant. The corneal donor in Alaska was a 3-year-old boy who had drowned. The corneas were harvested five days before use and stored in commercially available McCarey-Kaufman buffered medium containing gentamicin (100 μg/ml). Each patient received a single subconjunctival injection of gentamicin after transplantation. *Streptococcus pneumoniae* type 14 was isolated from conjunctival swabs of the infected eyes of both patients. The two cases in California occurred in two different cities. The donor was the same for each patient. The grafts were harvested three days before transplant and stored in McCarey-Kaufman medium containing 100 μg/ml of gentamicin. Each patient received a subconjunctival injection of gentamicin after the transplant. *Streptococcus pneumoniae* was also cultured from the two patients in California. The Eye Bank Association of America recommends routine culture of the corneoscleral rim before or at the time of surgery. Thus if there is clinical evidence of infection the culture results can be used as a guide to appropriate therapy. (14 references)—David Shoch

Nature

Retinoblastoma in transgenic mice. Windle, J. J., Albert, D. M., O'Brien, J. M., Marcus, D. M., Disteche, C. M., Bernards, R., and Mellon, P. L. (Regulatory Biol. Lab., Salk Inst. for Biol. Studies, 10010 N. Torrey Pines Rd., La Jolla, CA 92037). Nature 343:665, 1990.

Retinoblastoma, a malignancy of the eye occurring in young children, has been widely

studied as a model for genetic predisposition to cancer. This disease is caused by mutations in both alleles of an anti-oncogene (the retinoblastoma gene, Rb) that inactivate or eliminate RB encoded protein, $p105^{Rb}$ (refs 1 and 2). Here we report that expression of a viral oncogene, the simian virus 40 T antigen, in the retina of transgenic mice produces heritable ocular tumours with histological, ultrastructural and immunohistochemical features identical to those of human retinoblastoma. Furthermore, we demonstrate a specific association between $p105^{Rb}$ and T antigen in mouse retinoblastoma tumour cells. Thus, the occurrence of these tumours is *in vivo* evidence for oncogenesis due to the ocular-specific expression of an Rb-binding oncoprotein that can functionally inactivate the Rb protein. As an animal model for heritable retinoblastoma, these mice should allow the study of the ontogeny, pathogenesis and treatment of this malignant disease. (4 figures, 35 references)—Authors' abstract

New England Journal of Medicine

A controlled trial of azathioprine in Behçet's syndrome. Yazici, H., Pazarli, H., Barnes, C. G., Tüzün, Y., Özyazgan, Y., Silman, A., Serdaroğlu, S., Oğuz, V., Yurdakul, S., Lovatt, G. E., Yazici, B., Somani, S., and Müftüğlu, A. (Safa Sok, 17/43 Kadiköy, Istanbul, Turkey). N. Engl. J. Med. 322:281, 1990.

Cytotoxic agents have long been used in Behçet's syndrome, especially for eye involvement, but their effectiveness has been uncertain. We conducted a two-year randomized, placebo-controlled, double-blind trial of azathioprine (2.5 mg per kilogram of body weight per day) in Turkish men with Behçet's syndrome without eye disease (group 1; n = 25) or with eye disease (group 2; n = 48). Corticosteroid treatment remained available to all the patients.

The six patients withdrawn from the study because of severe eye disease were receiving placebo ($P < 0.001$). Azathioprine was superior to placebo in the prevention of new eye disease in group 1 (1 vs. 8 patients; $P < 0.01$) and in group 2 among the 14 patients who at entry had disease in only one eye ($P < 0.001$). There were fewer episodes of hypopyon uveitis (1 vs. 15; $P < 0.001$) among the group 2 patients who took azathioprine. The patients taking azathioprine also had less frequent oral ulcers, genital ulcers, and arthritis. There were no serious side effects attributable to azathioprine.

We conclude that azathioprine is effective in controlling the progression of Behçet's syndrome, especially its most serious manifestation, eye disease. (1 figure, 3 tables, 14 references)—Authors' abstract

Hyperostosis cranialis interna. A new hereditary syndrome with cranial-nerve entrapment. Manni, J. J., Scaf, J. J., Huygen, P. L. M., Cruysberg, J. R. M., and Verhagen, W. I. M. (Dept. Otorhinolaryngol., Univ. Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, Netherlands). N. Engl. J. Med. 322:450, 1990.

The proband was first seen at age 20 years because of a recurrent left facial nerve palsy of three weeks duration. She also had right vision of 4/300, a dense central scotoma, an afferent pupillary defect, and a pale optic nerve head. Her mother showed the same findings and in addition had eighth nerve impairment. Other members of the family showed variable involvement of the facial nerve but normal optic nerves. Radiologic examination disclosed intracranial hyperostosis and osteosclerosis of the calvaria and the base of the skull. In all cases the mandible and skeleton were normal. The authors classified this disorder as among the craniotubular hyperostoses and labeled it hyperostosis cranialis interna. (3 figures, 11 references)—David Shoch

Correction

In the article, "Recurrence of posterior polymorphous corneal dystrophy after penetrating keratoplasty," by S. Arthur Boruchoff, Mark J. Weiner, and Daniel M. Albert (Am. J. Ophthalmol. 109:323, March 1990), an error was introduced into the last sentence of the first paragraph of the Discussion. The sentence should read as follows: In some patients, the dystrophy may be accompanied by peripheral anterior synechiae and glaucoma, making clinical differentiation from iridocorneal-endothelial (*not epithelial*) syndrome difficult.[6-8]

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
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The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

European Contact Lens Society of Ophthalmologists: 20th Congress

The 20th European Contact Lens Society of Ophthalmologists Congress will be held on board the Scandinavian Seaways liner, commuting between Copenhagen and Oslo, Aug. 30–Sept. 1, 1990. For further information, write Ole Dithmer, M.D., Eye Department, Hvidovre Hospital, Kettegaard Allé 30, DK-2650 Hvidovre, Denmark.

Helsinki University Central Hospital: 30th Nordic Ophthalmological Meeting

The Helsinki University Central Hospital: 30th Nordic Ophthalmological Meeting will be held Aug. 25–28, 1991, in Helsinki, Finland. For further information, write Raine Mustonen, M.D., Department of Ophthalmology, University Central Hospital, Haartmaninkatu 4 C, 00290 Helsinki, Finland.

International Society of Ocular Trauma: Second International Congress

The International Society of Ocular Trauma: Second International Congress will be held April 2–5, 1992, in Geneva, Switzerland. For further information, write Elisha Bartov, M.D., Secretary of ISOT (International Society of Ocular Trauma), c/o Goldschleger Eye Institute, Sheba Medical Center, Tel-Hashomer 52621, Israel.

Baylor College of Medicine: 27th Annual Ophthalmology Alumni Association Meeting

The Baylor College of Medicine: 27th Annual Ophthalmology Alumni Association Meeting will be held June 8 and 9, 1990, at the Westin Oaks Hotel in Houston, Texas. For further information, write Bette Burkett, Cullen Eye Institute, Baylor College of Medicine, Houston, TX 77030; telephone (713) 798-5942.

Center for Sight, Georgetown University Medical Center: New Advances in Office and Outpatient Cosmetic and Reconstructive Surgery in Ophthalmology

The Center for Sight, Georgetown University Medical Center: New Advances in Office and Outpatient Cosmetic and Reconstructive Surgery in Ophthalmology Seminar will be held Oct. 18–20, 1990, at The Greenbrier in White Sulphur Springs, West Virginia. For further information and registration material, write Center for Sight, Georgetown University Medical Center, 3800 Reservoir Rd. N.W., Washington, DC 20007; telephone (202) 687-4952.

Humana Hospital—Lexington: Fifth Annual Multispecialty Oculoplastic Surgery Symposium

The Center for Advanced Eye Surgery at Humana Hospital—Lexington will sponsor the Fifth Annual Multispecialty Oculoplastic Surgery Symposium, Sept. 28 and 29, 1990, in Lexington, Kentucky. For further information, write Karen Heidorn, Center for Advanced Eye Surgery, Humana Hospital—Lexington, 150 N. Eagle Creek Dr., Lexington, KY 40509; telephone (606) 268-3754.

University of Illinois at Chicago: Second Annual Eye Trauma Symposium

The University of Illinois at Chicago: Second Annual Eye Trauma Symposium will be held July 19 and 20, 1990, in Chicago, Illinois. For further information, write UIC Eye Center (m/c 648), Catherine M. Brod, Program Director, 1855 W. Taylor St., Chicago, IL 60612; telephone (312) 996-4747.

Manhattan Eye, Ear and Throat Hospital: The Masters of Cataract Surgery Course

The Manhattan Eye, Ear and Throat Hospital: The Masters of Cataract Surgery Course will be held June 8 and 9, 1990, in New York, New York. For further information, write Francine Leinhardt, Course Coordinator, Manhattan Eye, Ear and Throat Hospital, 210 E. 64th St.,

New York, NY 10021; telephone (212) 838-9200, ext. 2776; FAX (212) 832-9126.

Pacific Presbyterian Medical Center and Pacific Vision Foundation: Corneal and Refractive Surgery—A Symposium Commemorating Max Fine, M.D.

Pacific Presbyterian Medical Center and Pacific Vision Foundation: Corneal and Refractive Surgery—A Symposium Commemorating Max Fine, M.D., will be held Sept. 21 and 22, 1990, in San Francisco, California. For further information, write Pacific Vision Foundation, 2340 Clay St., Suite 124, San Francisco, CA 94115; telephone (415) 923-3423.

Washington University School of Medicine: 30th Annual Eye Alumni Association Meeting

The Washington University School of Medicine: 30th Annual Eye Alumni Association Meeting will be held May 18 and 19, 1990, in St. Louis, Missouri. For further information, write Kathy Ryan, Box 8096, 660 S. Euclid Ave., St. Louis, MO 63110; telephone (314) 362-5722.

Western Association for Vitreoretinal Education: First Annual Meeting

The Western Association for Vitreoretinal Education: First Annual Meeting will be held July 16–19, 1990, in Maui, Hawaii. For further information, write Pacific Vision Foundation, Pacific Presbyterian Medical Center, 2340 Clay St., San Francisco, CA 94115; telephone (415) 923-3423.

Castroviejo Cornea Society: 1990 Officers

The Castroviejo Cornea Society elected the following officers for 1990: Jules Baum, president; James McCulley, vice president; Gary Foulks, executive secretary treasurer; and H. Dwight Cavanagh, immediate past president. New members of the Board of Directors are Juan Arentsen, Michael Cobo, George Stern, and Alan Sugar.

Association of University Professors of Ophthalmology: New Trustees Elected

The Association of University Professors of Ophthalmology elected the following: Thomas A. Weingeist, trustee; and Froncie A. Gutman and Irvin P. Pollack, affiliate trustees. Morton F. Goldberg, president, heads a Board of Trustees that includes Paul R. Lichter, John L. Keltner, Dan B. Jones, David E. Eifrig, Richard D. Richards, and Robert E. Kalina, executive vice president.

Personals

Elio Raviola

Elio Raviola has been appointed director of the Howe Laboratory of Ophthalmology at the Massachusetts Eye and Ear Infirmary. Raviola was named vice-chairman for research for the Department of Ophthalmology at Harvard Medical School where he is also the Bullard Professor of Neuroanatomy in the Department of Anatomy and Cell Biology.

David Shoch

Northwestern University awarded David Shoch the University Medal, its highest award to a graduate of the University, at a formal banquet in Chicago, April 7, 1990. Dr. Shoch received the doctorate of medicine and the doctorate of philosophy from Northwestern University, and served as professor and chairman of the Department of Ophthalmology.

INSTRUCTIONS TO AUTHORS

For the preparation of typescripts for THE AMERICAN JOURNAL OF OPHTHALMOLOGY

For more detailed information, see the Instructions to Authors published periodically in each volume, or write to Editorial assistant, American Journal of Ophthalmology, Suite 1415, 435 N. Michigan Avenue, Chicago, IL 60611.

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At the time of submission, a signed copy of the disclosure statement and copyright transfer published in THE JOURNAL each month must be included with the manuscript. No article or letter will be reviewed until this disclosure statement and copyright transfer, signed by each author in the order that each name appears on the title page, has been received. The transfer must also list the home address of each author and the telephone number of the corresponding author.

The manuscript must be original and may not contain data published previously or submitted for publication elsewhere. If the data were presented at a scientific meeting, the place, date of presentation, and auspices of the meeting should be stated on the title page.

Mechanical Preparation of the Typescript

The manuscript should be prepared in the style used by THE JOURNAL. Use 8½ × 11-inch heavy, white paper with a 1½-inch margin on all four sides. Paragraphs should be indented at least one-half inch. Use black, clearly legible type. Use letter-quality, not dot matrix, printing. Use block, not cursive type. (Use nothing smaller than 12 pitch or 11 point type.) Everything must be double-spaced. Do not type anything in all capitals. Do not use acronyms or abbreviations, except for standard measurements. Do not use vertical lines or underlining anywhere in the text. In the upper right-hand corner, identify each page with a number, first author's name, and an abbreviated title.

Submit an original and at least two duplicate copies of both the typescript and illustrations. Xerographic copies of the typescript are preferred to carbon copies. The manuscript should be arranged in the following order: title page; summary; text; references; legends; and tables. Each section should begin on a separate sheet.

Title Page

The title page is page 1. It should contain the title, a brief heading (no more than 60 characters and spaces) in the upper right hand corner, and each author's name with the highest academic degree. The department and institution where the study was performed should be indicated. Sponsoring organizations and grant support are acknowledged on the title page. The name and mailing address of the author to whom requests for reprints should be directed must be indicated.

Summary

Each paper must have a summary that specifically condenses the content of the paper in 150 words or less. The summary must be written so that the message of the paper can be understood independently. It should include the main clinical or research data and findings but exclude speculation.

References

The corresponding author is responsible for complete and accurate references, including proper capitalization and accent marks used in foreign-language publications. References must be numbered consecutively, according to their appearance in the text. Extensive bibliographic reviews are not acceptable. The names of all authors must be included; THE JOURNAL does not use the term et al. Index Medicus abbreviations are used. Personal communications and references to studies in progress or not yet accepted for publication must be incorporated into the text without reference numbers.

Illustrations

Graphs, diagrams, and line drawings must be prepared by a professional artist using India ink.

They must not be mounted. Each illustration should be numbered and cited consecutively in the text. The illustration number, an arrow indicating the top, and the first author's name should be included on a label on the back.

Each illustration must have a legend that describes the significance of what is shown. Legends should be typed consecutively on a page (separate from the illustrations themselves); the legend or illustration number should never be incorporated into the illustration. Legends should be typed in the form used by THE JOURNAL.

Photographs must have a glossy finish and a sharp contrast. All labels, arrows, and the like must be professionally applied. In a series of illustrations, all parts should be oriented in the same direction. Photographs should be the same size or larger than the intended reproductions. Illustration widths in THE JOURNAL are 3 inches for one column and 6½ inches for two columns.

Visual field charts used in THE JOURNAL will be supplied to authors without charge upon request. Write to the Editorial Assistant.

Color

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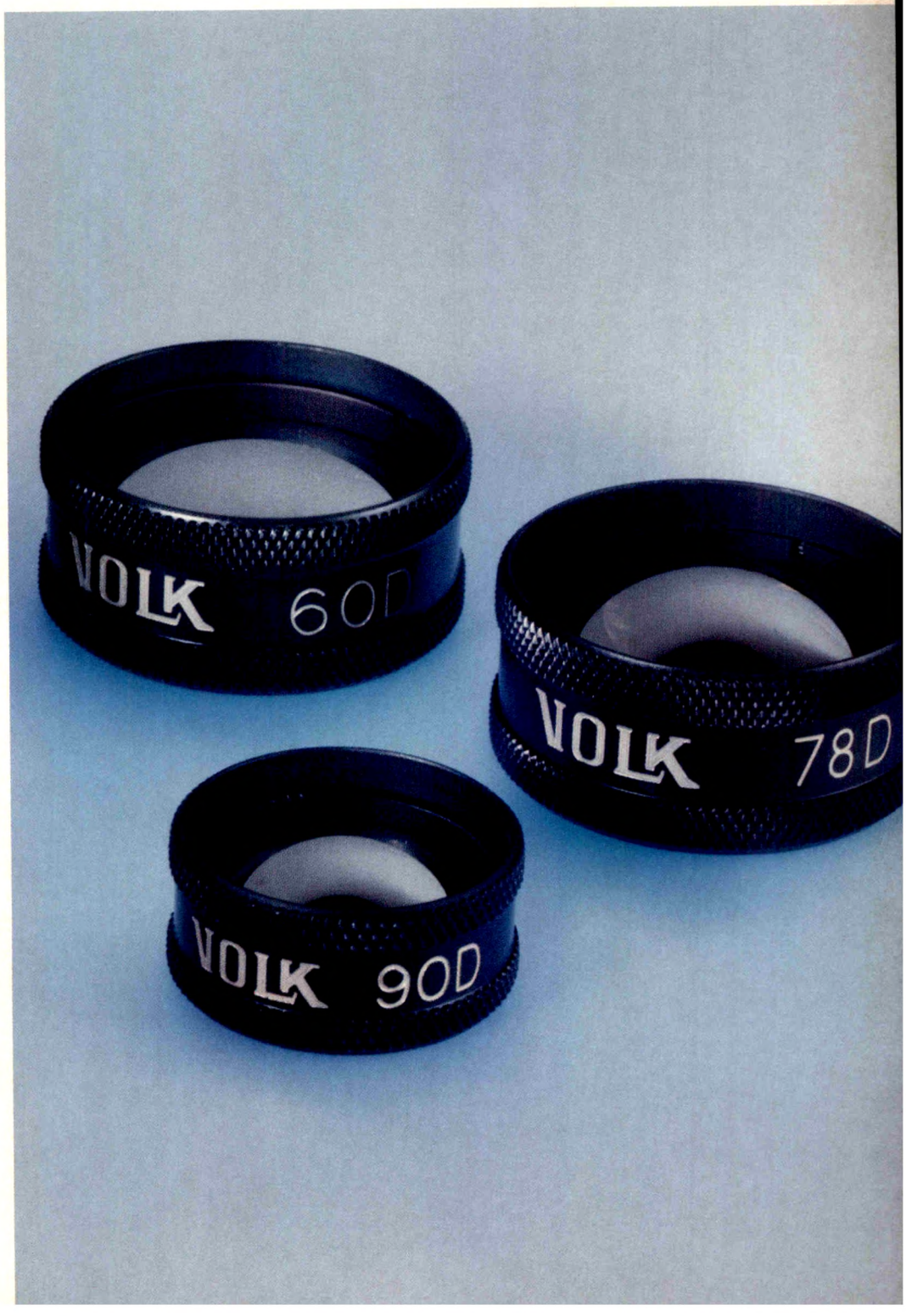

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Variable Genotype of Leber's Hereditary Optic Neuropathy Patients

Marie T. Lott, M.A., Alexander S. Voljavec, M.D., and Douglas C. Wallace, Ph.D.

Leber's hereditary optic neuropathy is caused by a single nucleotide change in the mitochondrial deoxyribonucleic acid (mtDNA). Each cell contains thousands of mitochondrial DNA molecules. We demonstrated that in certain isolated instances, the proband and close maternal lineage relatives can have mixtures of mutant and normal mitochondrial DNA molecules (heteroplasmy). The proportion of mutant mitochondrial DNA molecules was found to shift markedly across generations and within the tissues of an individual. One unaffected mother had 65% mutant mitochondrial DNA molecules whereas her affected son had essentially 100% mutant mitochondrial DNA molecules. Two affected individuals had predominantly mutant mitochondrial DNA in their blood, but significant normal mitochondrial DNA in their hair. The demonstration of heteroplasmy within maternal lineages and affected individuals means that the successful determination of the mitochondrial DNA genotype of a family or patient with Leber's hereditary optic neuropathy requires testing of more than one family member and more than one tissue from each individual.

Accepted for publication March 23, 1990.

From the Departments of Biochemistry (Ms. Lott and Dr. Wallace), Nephrology (Dr. Voljavec), Pediatrics (Dr. Wallace), and Neurology (Dr. Wallace), Emory University School of Medicine, Atlanta, Georgia. This study was supported by National Institutes of Health grant NS21328, a Muscular Dystrophy Clinical Research grant, and an Emory Neuromuscular Center grant (Dr. Wallace).

Reprint requests to Douglas C. Wallace, M.D., Emory University School of Medicine, Department of Biochemistry, 3031 Rollins Research Ctr., Atlanta, GA 30329.

LEBER'S HEREDITARY OPTIC NEUROPATHY is a disease of young adults characterized by bilateral loss of central vision. In families with multiple affected individuals, all are related through the maternal lineage,[1,2] which suggests that Leber's hereditary optic neuropathy is caused by a mitochondrial DNA mutation.[3,4] We confirmed this conclusion by identifying a single guanine to adenine transition mutation in the mitochondrial DNA (mtDNA) at nucleotide position 11778, which causes this disease. This mutation converts the 340th amino acid in the reduced nicotinamide adenine dinucleotide (NADH) dehydrogenase subunit 4 (ND4) gene from an arginine to a histidine. It also eliminates a recognition site for the restriction endonuclease SfaNI, thus providing a simple and rapid molecular diagnostic test for this disease.[5]

See also p. 726.

Analysis of the mitochondrial DNA molecules of Leber's hereditary optic neuropathy patients of different ethnic groups has indicated that this mutation has occurred many times independently.[6,7] Because each human cell has thousands of mitochondrial DNA molecules,[8] the original mutant molecule must increase from one mutant among thousands of normal molecules to a substantial percentage of mutant molecules before a neuropathy would ensue. Thus, a patient who has visual loss must be preceded by ancestors with heteroplasmy (mixed mutant and normal molecules).[9] Because the normal molecules in the patients' cells would reduce the impact of the mutant genotype, detection and quantitation of heteroplasmy is of great importance in the diagnosis and counseling of these patients.[10]

We identified patients and their maternal relatives who were heteroplasmic for the Leber's

hereditary optic neuropathy mutation. The ratio of mutant and normal mitochondrial DNA molecules can differ markedly both in the maternal lineages of pedigrees and between somatic tissues. The replicative segregation of heteroplasmic mitochondrial DNA molecules may play an important role in clinical variability of this unique form of optic neuropathy.

Material and Methods

Whole blood, platelet or lymphocyte fractions, lymphoblastoid cell lines, and hairs (0.5 to 1 cm of root end from four to five hairs) were studied in patients with Leber's hereditary optic neuropathy and their maternal relatives.

Blood was collected in either sodium heparin or acid citrate dextrose after obtaining informed consent from the patients. Whole blood (200 μl) was removed for immediate DNA extraction; the remainder of the sample was fractionated, and the lymphocytes were transformed with Epstein-Barr virus[11] to establish permanent cell lines. Blood samples were spotted onto filter paper and allowed to air dry. Hair samples included the root and shaft and were stored at room temperature.

DNA was extracted from whole blood (200 μl), small platelet or lymphocyte fractions (cells from 1 ml), blood spots (1 cm in diameter), and hair (0.5 to 1 cm of the root end of four to five hairs). Lysis buffer [25 mM Tris(hydroxymethyl)-aminomethane (Tris), pH 8.0, 1 mM ethylenediaminetetraacetic acid (EDTA), 0.5% sodium dodecyl sulfate, and 10 μg proteinase K] was added to the samples to a final volume of 400 μl before overnight incubation at 55 C. Samples were then heated to 95 C for ten minutes, cooled to room temperature, and incubated with 200 μg of ribonuclease A for 15 minutes. Sodium dodecyl sulfate and proteins were precipitated with 2.55 M potassium acetate, and the supernatant was loaded onto an anion-exchange affinity column (Quiagen, Inc., Studio City, California). Contaminating proteins, heme, heparin, and RNA were eluted by following the manufacturer's recommendations, and the recovered DNA was used for amplification with the polymerase chain reaction.[12] From most preparations, less than 1% of the sample was used as a template for a 100-μl polymerase chain reaction. For suboptimal samples such as hair or dried blood spots, however, 20% to 50% of the preparation was used.

Two different DNA fragments were prepared, which encompassed the nucleotide position 11778 Leber's marker: a 1435 base pair fragment (representing nucleotide positions 11141 to 12576) and a 212 base pair fragment (representing nucleotide positions 11673 to 11873). Forward (→) and reverse (←) oligonucleotide primers (Microchemical Facility of Molecular Biology, Emory University, Atlanta, Georgia) for the larger fragment were located at nucleotide positions 11141 to 11158(→) and nucleotide positions 12576 to 12557(←). Primers for the smaller fragment were located at nucleotide positions 11673 to 11691(→) and nucleotide positions 11873 to 11851(←). For suboptimal samples (hemolyzed blood samples, dried blood, or hair), the smaller fragment was more easily generated. Thermal profiles consisted of 35 cycles of denaturing for one minute at 94 C, annealing for 30 seconds at 53 C for the 1435 base pair primers, or 59 C for the 212 base pair primers, and extension for one minute at 72 C.

Enriched mitochondrial DNA was obtained from Epstein-Barr virus transformed cell lines of a family with Leber's hereditary optic neuropathy (EUH297, EUH296, EUH321, EUH322, EUH323), a control Leber's patient (CDW0092/GM10742), and a normal control subject (CDW0099). Approximately 3×10^7 cells were resuspended in 3 ml of isotonic buffer [2.5 mM EDTA, 20 mM N-[2-Hydroxyethyl] piperazine-N'-[2-ethanesulfonic acid] (HEPES), 137 mM NaCl, 5 mM KCl, 0.7 mM dibasic sodium phosphate, 6 mM dextrose, pH 7.1], an equal volume of lysis buffer (0.01 M HEPES, 0.01 M EDTA, 1% sodium dodecyl sulfate, pH 7.0) was added and the mixture allowed to sit 20 minutes at room temperature to lyse the cells. Sodium chloride was added to a final concentration of 1 M, and the solution was chilled at 4 C overnight and clarified.[11] The RNA was removed by addition of 200 μg of ribonuclease A. Proteins were removed by further lysis with 0.5% sodium dodecyl sulfate followed by digestion at 55 C with 10 μg/ml of proteinase K. Cellular debris and sodium dodecyl sulfate were precipitated by the addition of one half volume 2.55 M potassium acetate; the samples were brought to less than 0.85 M NaCl with 50 mM 3-(6-methoxyquinolino) propane sulfonate (MDPS), pH 7.0, and the DNA purified with an anion-exchange affinity column.

For genomic Southern blots, 4 μg of enriched mitochondrial DNA from the lymphoblast cell lines was digested with 1 unit of the restriction endonuclease SfaN1 (New England Biolabs, Beverly, Massachusetts) at 37 C for eight to ten

hours. The digested DNA was fractionated on 1.4% Tris-borate agarose gels and transferred onto nylon membrane (Magnagraph, MSI, Westboro, Massachusetts). To test for the Sfa N1 site in the 212 base pair DNA fragment, 200 to 300 ng of amplified ND4 DNA (10% to 20% of a polymerase chain reaction) was digested with 1 unit of the enzyme, and the fragments were separated on an agarose gel containing ethidium bromide and detected by ultraviolet fluorescence. To check for accidental cross-contamination of DNA, a sample of H_2O without DNA was carried through the entire extraction, amplification, and analysis process.

Southern hybridization probes for the ND4 gene were prepared by random primer extension[13,14] of the 1435 base pair ND4 polymerase chain reaction fragment with digoxigenen-uridine-5'triphosphate, gel purified using Gene Clean II (Bio 101, Inc., La Jolla, California) and the hapten-labeled DNA detected with the Genius labeling and detection system (Boehringer Mannheim, Indianapolis, Indiana). The 1435 base pair fragment was directly sequenced using asymmetrically amplified mitochondrial DNA as templates.[15,16]

Agarose gels with ethidium bromide–stained DNA were photographed with Polaroid 55 P/N film. Quantitative densitometry was performed on the negatives with an UltroScan XL Laser Densitometer equipped with Gel-Scan XL software package, version 2.0 (Pharmacia LKB Biotechnology, Piscataway, New Jersey). Densitometry was performed on positive film images of the hybridized filters.

Results

To detect and quantitate mutant and wild type mitochondrial DNA molecules in family members with Leber's hereditary optic neuropathy, a 1435 base pair polymerase chain reaction fragment was prepared with the polymorphic SfaNI site in the center. SfaNI digestion of this fragment bearing the Leber's hereditary optic neuropathy mutation generates a 1317 base pair fragment (nucleotide positions 11141 to 12456) and a 119 base pair fragment (nucleotide positions 12456 to 12576). This latter fragment was allowed to migrate off the gel. Digestion of the fragment from wild type mitochondrial DNA molecules cuts the 1317 base pair fragment into 638 base pair (nucleotide positions 11141 to 11778) and 679 base pair (nucleotide positions 11778 to 12456) fragments. Because the 638 and 679 base pair fragments from wild type mitochondrial DNA initially superimpose on the gel, the DNA fluorescence in the 638/660 base pair and 1317 base pair bands are directly proportional to the number of wild type and mutant molecules.

The blood cell mitochondrial DNA molecules of most isolated Leber's hereditary optic neuropathy cases gave a single band at nucleotide

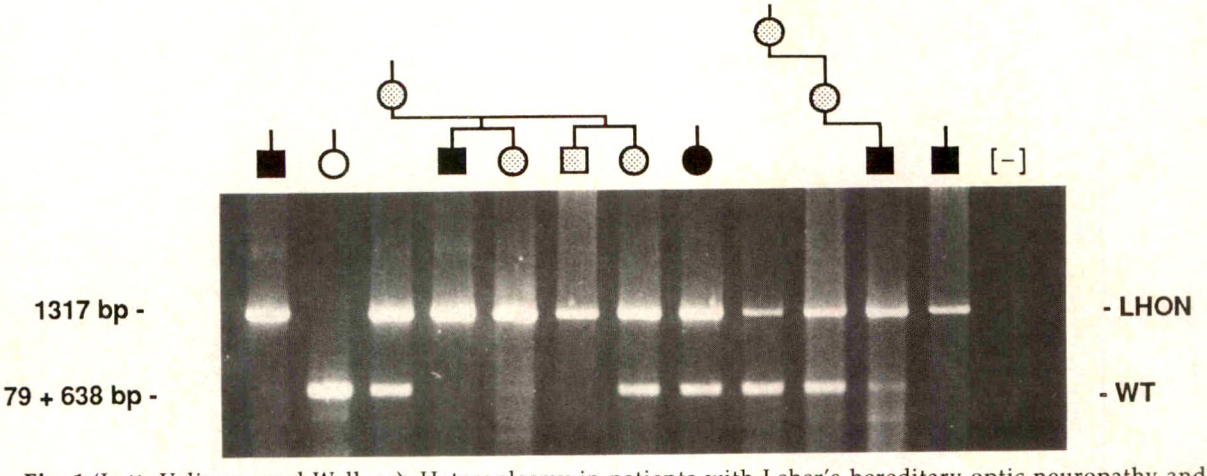

Fig. 1 (Lott, Voljavec, and Wallace). Heteroplasmy in patients with Leber's hereditary optic neuropathy and unaffected maternal lineage relatives. Mutant (Leber's hereditary optic neuropathy) and normal (wild type) mitochondrial DNA molecules detected by polymerase chain reaction amplification of a 1435 base pair ND4 fragment, digestion with SfaNI, and analysis by electrophoresis visualized by ethidium bromide staining. LHON indicates Leber's hereditary optic neuropathy; WT, wild type; bp, base pairs; solid symbols, blind subjects; stippled symbols, maternal lineage relatives who retained full vision (unaffected carriers). [–] indicates lane with H_2O sample only, a contamination control.

position 1317 and hence were essentially homoplasmic for the mutation (Fig. 1, lanes 1 and 12 from left). Similarly, random normal controls gave a band at about 638/660 base pair consistent with homoplasmic wild type (Fig. 1, lane 2). By contrast, occasional isolated cases gave both 1317 and 638/660 base pair bands indicating heteroplasmy (Fig. 1, lane 8). Densitometric analysis indicated that blood cells from this female patient with Leber's hereditary optic neuropathy contained 71% mutant and 29% wild type mitochondrial DNA molecules.

To determine if homoplasmic, isolated Leber's probands might have heteroplasmic relatives, we analyzed the blood cell mitochondrial DNA molecules of the three siblings and mother of one patient (Fig. 1, lanes 3 to 7). The mother (Fig. 1, lane 3) proved strongly heteroplasmic with 65% mutant and 35% wild type mitochondrial DNA molecules. One of the sisters (Fig. 1, lane 7) was comparably heteroplasmic (64% mutant, 36% wild type). The other sister (Fig. 1, lane 5) had about 7% normal mitochondrial DNA molecules and the other brother (Fig. 1, lane 6) had essentially pure mutant mitochondrial DNA molecules. Hence, in this family, three of the four children have segregated to essentially homoplasmic Leber's mutant mitochondrial DNA in one generation and one daughter retained the heteroplasmy of the mother.

In a second family, the proband was observed to be mildly heteroplasmic with only about 25% wild type mitochondrial DNA molecules (Fig. 1, lane 11). Analysis of his unaffected mother disclosed 59% mutant and 41% wild type mitochondrial DNA molecules (Fig. 1, lane 10), whereas his grandmother had 42% mutant and 58% wild type mitochondrial DNA molecules (Fig. 1, lane 9). Hence, in this family, the Leber's hereditary optic neuropathy mutation progressively increased in frequency over three generations.

Because the polymerase chain reaction amplifies even trace amounts of contaminating DNA to easily detectable levels, we confirmed the presence of heteroplasmy in genomic, nonamplified DNA by Southern blot analysis of lymphoblastoid cell lines from the two-generation heteroplasmic family (Fig. 1, lanes 3 to 7). Cellular DNA preparations enriched for mitochondrial DNA were digested with SfaNI, and the fragments were separated by agarose gel and detected by Southern blotting and hybridization with an ND4 probe (Fig. 2). The diagram

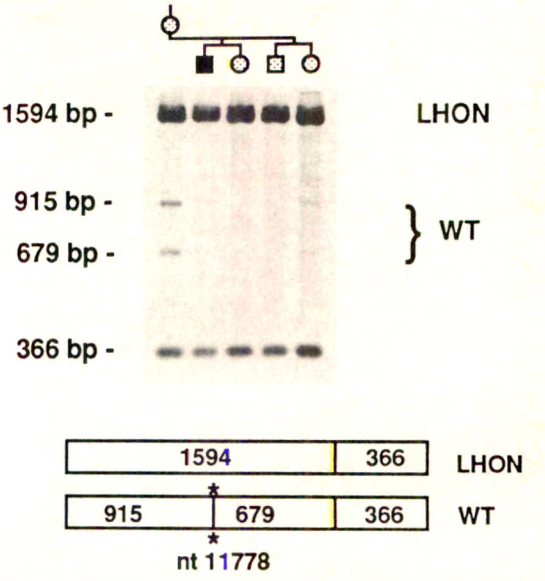

Fig. 2 (Lott, Voljavec, and Wallace). Heteroplasmy detected by digestion of genomic DNA with SfaNI and detection of ND4 fragments by Southern blot hybridization. Upper panel, LHON indicates Leber's hereditary optic neuropathy; WT, wild type; bp, base pairs; solid symbols, blind subjects; stippled symbols, maternal lineage relatives who retained full vision (unaffected carriers). Lower panel, Restriction map of fragments detected by the ND4 hybridization probe. Vertical lines indicate SfaNI restriction sites; *, site of Leber's hereditary optic neuropathy mutation; numbers in boxes, lengths of restriction fragments in nucleotide pairs.

at the bottom of Figure 2 illustrates the expected fragments: 1594 base pair for Leber's hereditary optic neuropathy mitochondrial DNA molecules, 915 base pair and 679 base pair for wild type mitochondrial DNA molecules with a common fragment of 366 base pair. All family member mitochondrial DNA preparations yielded predominantly the 1594 base pair Leber's hereditary optic neuropathy fragment, but the mother's mitochondrial DNA also produced a substantial proportion of the 915 base pair and 679 base pair wild type fragments, as did the youngest daughter's, but to a lesser extent. Hence, the heteroplasmy detected by SfaNI digestion of polymerase chain reaction amplified mitochondrial DNA is present in the original patient mitochondrial DNA. Differences in percentage between Figures 1 and 2 probably reflect replicative segregation during preparation of the lymphoblastoid cell lines.

To confirm that the heteroplasmy detected by SfaNI digestion results from a mixture of mito-

chondrial DNA molecules having an adenine or a guanine at nucleotide position 11778, we directly sequenced polymerase chain reaction amplified mitochondrial DNA from the mother (Fig. 1, lane 10) of the three-generation pedigree. The direct sequence disclosed both an adenine (Leber's hereditary optic neuropathy) and a guanine (wild type) at position 11778 (Fig. 3). Hence, the heteroplasmy detected by SfaNI digestion reflects heteroplasmy at the mitochondrial DNA nucleotide sequence level. Comparable results have been obtained for the mother (Fig. 1, lane 3) and daughter (Fig. 1, lane 7) of the two-generation pedigree.

To determine if heteroplasmic mitochondrial DNA populations segregate during mitosis as well as meiosis, the proportion of Leber's hereditary optic neuropathy and wild type mitochondrial DNA molecules were compared in the blood (mesoderm) and hair (ectoderm) of several heteroplasmic individuals. One male proband had predominantly Leber's hereditary optic neuropathy mitochondrial DNA in his blood with a small amount of wild type mitochondrial DNA detectable only by the more sensitive Southern blot (Fig. 4, lane 4, lower panel). When hair follicles of this individual were examined, however, they were found to contain a high percentage of wild type mitochondrial DNA molecules with a smaller percentage of mutants (Fig. 4, lane 3, lower panel). For comparison, two female carriers homoplasmic for the Leber's hereditary optic neuropathy mutation are shown (Fig. 4, lanes 1 and 2). A second proband (Fig. 5, lanes 1 and 2) also had a predominance of mutant mitochondrial DNA in the blood and wild type in the hair. However, a third independent proband (Fig. 5, lanes 3 and 4) had predominantly mutant mitochondrial DNA molecules in both the blood and hair, with wild type mitochondrial DNA being detectable only by the more sensitive Southern blotting.

Differences between blood and hair were also observed in the three-generation pedigree of Figure 1 (Fig. 5, lanes 5 to 10). The grandmother and mother had comparable proportions of Leber's hereditary optic neuropathy and wild type mitochondrial DNA molecules in the two tissues (Fig. 5, lanes 5 and 8, 6 and 9). The proband (lanes 7 and 10), however, had substantially more wild type mitochondrial DNA in the hair than in the blood. Hence these results show that segregation of heteroplasmic mitochondrial DNA molecules occurs during the mitotic replication of development as well as during the meiotic replication of sexual reproduction.

Discussion

The discovery of heteroplasmy of the Leber's hereditary optic neuropathy mutation in our pedigrees confirms the recent observation of Holt, Miller, and Harding.[17] Further, our demonstration of the accompanying rapid meiotic and mitotic segregation provides one explanation for the variability in expression of the mutation between members of the same family. Because the presence of wild type mitochondrial DNA molecules would reduce the extent of the respiratory complex I deficiency of Leber's hereditary optic neuropathy patients, individuals whose optic nerve cells were heteroplasmic would be less likely to lose their vision.

Because meiotic segregation can result in major differences in the proportion of mutant mitochondrial DNA molecules between sib-

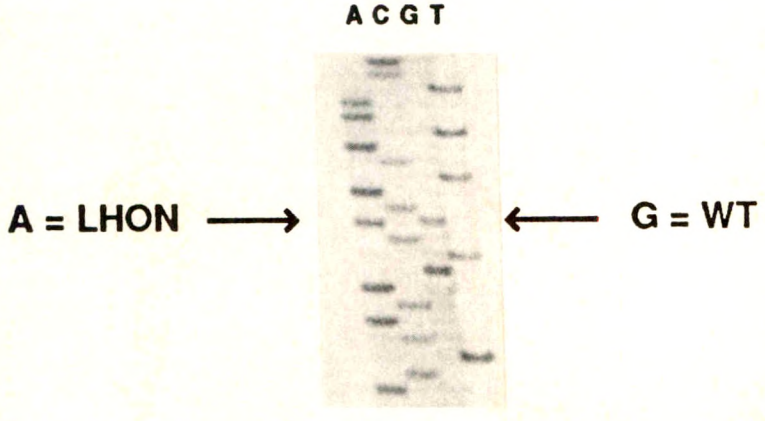

Fig. 3 (Lott, Voljavec, and Wallace). Direct sequencing of polymerase chain reaction amplified mitochondrial DNA from a heteroplasmic individual. DNA was prepared from the blood of the individual in lane 10 of Figure 1. The A C G T (adenine, cytosine, guanine, and thymine) indicate the bases detected in each lane of the sequencing ladder read vertically from bottom (5′) to top (3′). The heteroplasmic base is indicated. LHON indicates Leber's hereditary optic neuropathy; WT, wild type.

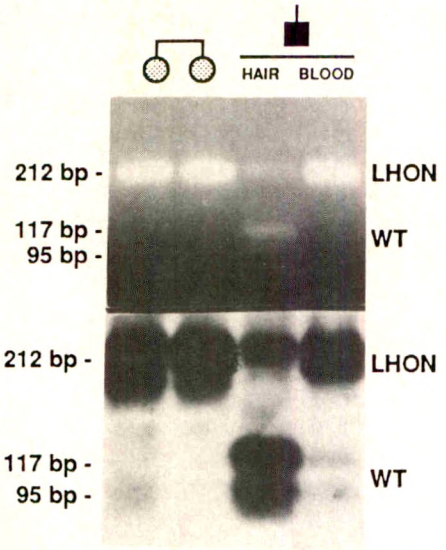

Fig. 4 (Lott, Voljavec, and Wallace). Heteroplasmy detected in the blood and hair from a patient. Upper panel, Heteroplasmy detected by polymerase chain reaction amplification of the 212 base pair ND4 fragment, digestion with SfaNI, and analysis by electrophoresis and ethidium bromide staining. Lower panel, Analysis of fragments from the upper panel by Southern blot and hybridization with the ND4 probe. Lanes 1 and 2 are blood cell DNA molecules from carriers of an independent lineage who have predominantly mutant mitochondrial DNA molecules. Lanes 3 and 4 are hair and blood from the proband. LHON indicates Leber's hereditary optic neuropathy; WT, wild type; bp, base pairs; solid symbols, blind subjects; stippled symbols, maternal lineage relatives who retained full vision.

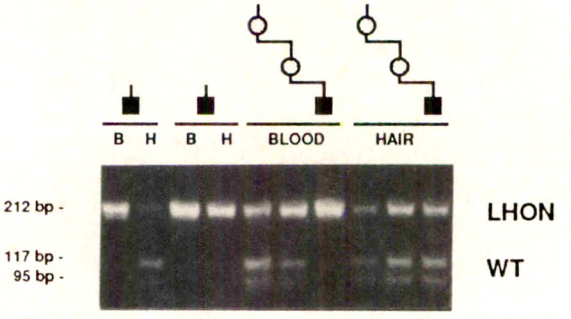

Fig. 5 (Lott, Voljavec, and Wallace). Heteroplasmy detected in the blood and hair from two independent probands and the members of the three-generation family. Heteroplasmy assessed as in the upper panel of Figure 4. The three generation pedigree is the same as that in Figure 1. LHON indicates Leber's hereditary optic neuropathy; WT, wild type; bp, base pairs; solid symbols, blind subjects; stippled symbols, maternal lineage relatives who retained full vision; B, blood; H, hair.

lings of the same family, some individuals will be genetically predisposed to visual loss and others will not. Further, because mitotic segregation can result in radical differences in the mitochondrial DNA genotype between tissues of the same individual, genotypic analysis of the mitochondrial DNA molecules of a single tissue such as blood is not necessarily indicative of the mitochondrial DNA genotype of the optic nerve and a reliable predictor of neuropathy. To increase the reliability of a genetic determination of Leber's hereditary optic neuropathy, individuals in the maternal lineage must be tested, and cells from several tissues (blood, hair, buccal mucosa, urinary tract epithelia) must be analyzed.

The rapid meiotic segregation rate of the heteroplasmic family members with Leber's hereditary optic neuropathy is comparable to that which has been described for mitochondrial DNA restriction fragment length polymorphisms along bovine maternal lineages.[18-20] This suggests that heteroplasmy may not be maintained for many generations. Additionally, large Leber's hereditary optic neuropathy pedigrees with many affected individuals would tend toward a homoplasmic mutant,[5] thus accounting for the repeated transmission of the trait along the maternal lineage. By contrast, some isolated cases may represent the first clinical manifestation of a new mutation and, being closer to the origin of the Leber's hereditary optic neuropathy mitochondrial DNA mutation, more likely to be heteroplasmic.

The rapid somatic segregation of the Leber's hereditary optic neuropathy mitochondrial DNA is surprising. Somatic cells have thousands of mitochondrial DNA molecules, and the equal division of the cell at cytokinesis should mean that each daughter cell would have a mitochondrial DNA genotype similar to that of the parental cell. Intracellular genetic drift of mitochondrial DNA proportion was thus expected to be slow and the mitochondrial DNA genotype between tissues similar.

These data on heteroplasmic Leber's hereditary optic neuropathy patient blood and hair, however, do not support this view, because the mitochondrial DNA genotypes were found to differ drastically. This suggests that some additional factor may contribute to the extent of

mitotic segregation in these patients. One possibility is that the cells of the tissues examined are mitotically active and therefore have had a greater opportunity to undergo mitotic segregation. Alternatively, the number of segregating mitochondrial DNA units is much smaller than the number of mitochondrial DNA molecules. Because segregating units might represent physically associated groups of mitochondrial DNA molecules (as in a mitochondrion) the smaller number of mitochondria to be distributed to daughter cells would increase the sampling error at cytokinesis and thus the effective rate of mitochondrial DNA segregation. It is clear that we must know more about the genetics of the mitochondrial DNA and Leber's hereditary optic neuropathy before we will be able to use molecular genotypes to make accurate predictions about clinical phenotypes.

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Septo-Optic Dysplasia in Two Siblings

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We treated two siblings, a sister and brother, who had features of septo-optic dysplasia, including bilateral optic nerve hypoplasia, absent septum pellucidum, and partial pituitary insufficiency. Additionally, midline central nervous system abnormalities of the corpus callosum and cerebellum were shown. The familial occurrence of this disorder raises the possibility of autosomal-recessive inheritance.

SEPTO-OPTIC DYSPLASIA, as first described by de Morsier,[1] is characterized by an absent septum pellucidum, a primitive optic vesicle, and dysplasia of the optic nerve, chiasm, and optic tracts. Hoyt and associates[2] noted that septo-optic dysplasia could be associated with hypopituitary dwarfism. Septo-optic dysplasia occurs more commonly in firstborn children[3] and children born to young mothers.[4] We treated two siblings who had the features of septo-optic dysplasia, representing a familial occurrence of this disorder.

Case Reports

Case 1

Patient 1, a girl, was the firstborn child of healthy, nonconsanguineous parents. The family history was noncontributory. The 24-year-old mother had an uneventful pregnancy and denied exposure to alcohol or drugs. The child was delivered vaginally at term with Apgar scores of 9, 9. The infant had an uncomplicated hospital course and was discharged after two days.

Congenital anomalies noted in the patient during the neonatal period included left metatarsus adductus, congenital hip dysplasia, and torticollis with a left head-tilt. At 6 weeks of age, she followed objects poorly.

At 5 months of age, the child was referred to us for evaluation of suspected visual impairment. Her growth included a weight of 7.8 kg (90th percentile), a height of 65 cm (60th percentile), and a head circumference of 44.5 cm (95th percentile). Neurologically, the patient was delayed with poor head control and an inability to roll over.

The ophthalmologic examination disclosed a visually inattentive infant, in whom optokinetic nystagmus could not be elicited. The pupils did not react to light, either directly or consensually. Intermittent upbeat nystagmus and an esotropic deviation were present. The ophthalmoscopic examination disclosed severe bilateral optic nerve hypoplasia (Fig. 1). A flash visual-evoked response was unrecordable bilaterally.

Results of the patient's karyotype and thyroid function tests were normal. The growth hormone response to an arginine and L-dopa challenge was absent. The electroencephalogram showed multiple potentially epileptogenic foci. Brainstem auditory-evoked responses were normal. A computed tomographic scan of the head showed lateral splitting of the leaves of the septum pellucidum, a dilated and elevated third ventricle, partial agenesis of the corpus callosum, and a large posterior fossa cyst that connected with an enlarged fourth ventricle (Fig. 2). A diagnosis of septo-optic dysplasia was made.

At 17 months of age, the patient began to have generalized tonic-clonic seizure episodes, which were partially controlled on carbamazepine therapy.

Hypothyroidism was diagnosed at 23 months of age. The patient was started on a regimen of

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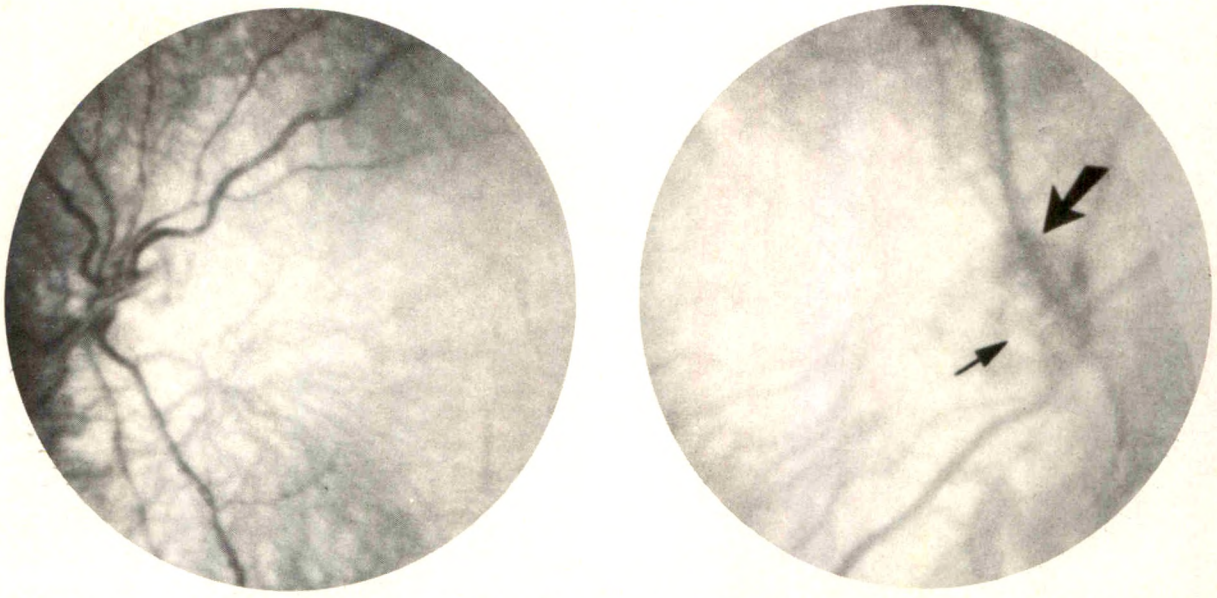

Fig. 1 (Benner and associates). Patient 1. Left, Right eye; right, left eye. Bilateral optic nerve hypoplasia. Small arrow marks the border of the true optic disk, whereas the large arrow demonstrates the peripapillary border area, which is slightly pigmented.

0.05 mg/day of levothyroxine sodium for hormonal replacement. She was still unable to roll over, but she was now able to maintain head control.

At 3 years of age, after a prolonged seizure episode, another computed tomographic scan was performed. The scan showed further enlargement of the ventricles consistent with hydrocephalus. The patient underwent a successful ventriculoperitoneal shunt. Valproate sodium was later added to the regimen in an attempt to control her persistent seizure activity, but it was not successful.

The patient was again hospitalized at 4½ years of age after an episode of status epilepticus. A magnetic resonance imaging scan of the head was performed, which showed hypoplasia of the anterior half and agenesis of the posterior half of the corpus callosum, lateral splitting of the leaves of the septum pellucidum to the laterally displaced bodies of the fornix, and a dilated third ventricle (Fig. 3). The cerebellum was hypoplastic with partial agenesis of the vermis. A large cystic space in the posterior fossa connected with the fourth ventricle (Fig. 4).

Case 2

Patient 1 was 3½ years old when her brother, Patient 2, was born. Pregnancy and delivery were again uneventful, and the mother denied exposure to any teratogenic substances.

The patient's mother became concerned about the patient's visual function after several weeks of life. At 9 weeks of age, he was examined at our institution. The child's weight was 6.4 kg (95th percentile), his height was 61 cm (95th percentile), and his head circumference was 40 cm (90th percentile). Neurologic evaluation suggested a moderate developmental delay, mild diffuse hypotonia, a head lag, and the absence of the obligate tonic neck and Moro reflexes.

An ophthalmologic examination performed when the boy was 10 weeks old disclosed poor visual attention. The pupillary light reactions were absent in both eyes, both direct and consensually. His eye movements were roving in character, and he showed an exotropic deviation. Ophthalmoscopic examination disclosed severe bilateral optic nerve hypoplasia. The flash visual-evoked response was absent bilaterally.

A computed tomographic scan of the head showed agenesis of the corpus callosum, lateral splitting of the septum pellucidum, and enlarged occipital horns of the lateral ventricles. A large posterior fossa cyst connected with the fourth ventricle. Baseline amino acid, metabol-

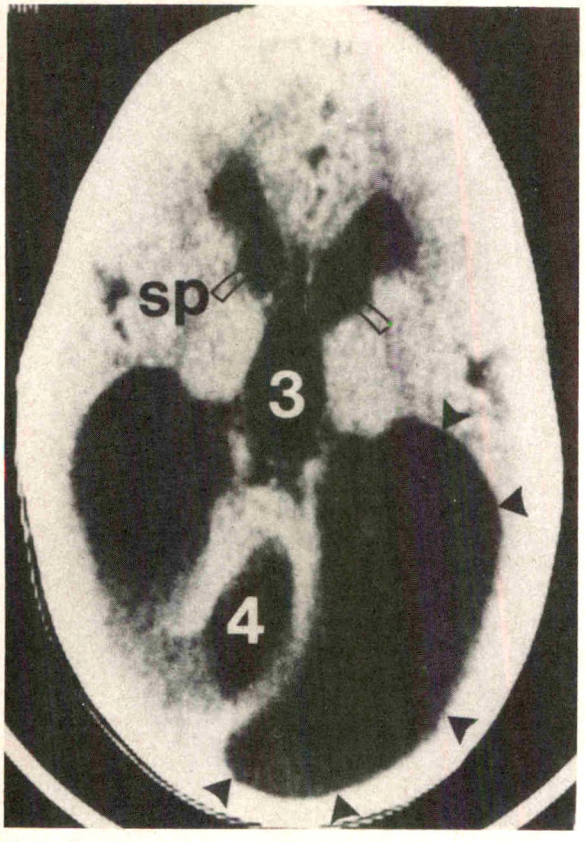

Fig. 2 (Benner and associates). Patient 1. Axial computed tomographic scan shows dilated third ventricle with laterally deviated septi pellucidi (SP). The dilated fourth ventricle connects with a large posterior fossa cyst (arrowheads).

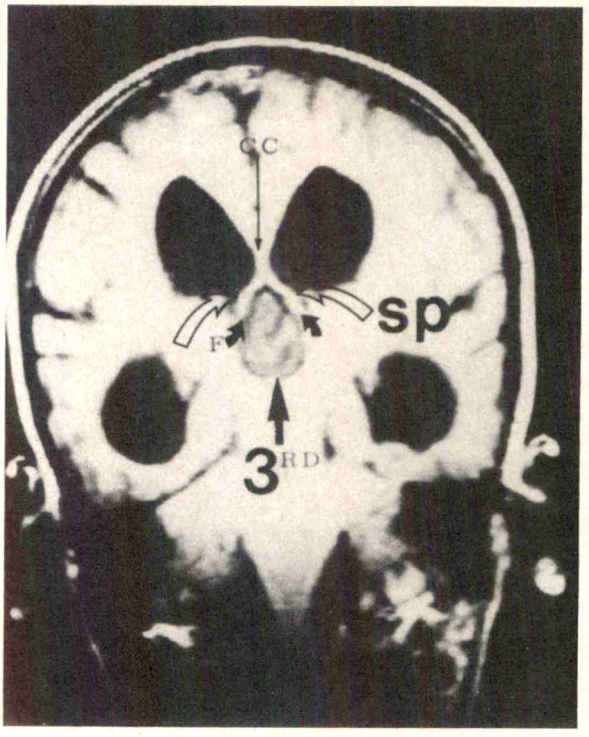

Fig. 3 (Benner and associates). Patient 1. Coronal magnetic resonance image shows hypoplastic corpus callosum (CC) that is joined by leaves of the laterally deviated septi pellucidi (SP) to the separated fornices (F). Note the dilated third ventricle and the enlarged occipital horns of the lateral ventricles of the lateral ventricles.

ic, and endocrinologic test results were normal. A diagnosis of septo-optic dysplasia was made.

At 9 months of age, the patient began to have petit mal seizures with loss of postural tone. A regimen of valproate sodium was started, but the seizures remained poorly controlled. A magnetic resonance imaging scan of the head was performed, which showed hypoplasia of the caudal half of the corpus callosum, an elevated third ventricle, lateral splitting of the leaves of the septum pellucidum, and enlarged occipital horns of the lateral ventricles. Additionally, the cerebellum was hypoplastic with partial agenesis of the vermis, through which there was connection with an enlarged cisterna magna (Figs. 5 and 6).

At 1 year of age, the patient's weight had dropped to the 60th percentile. Arginine, L-dopa, and insulin stimulation tests for growth hormone were recommended, but consent was not obtained.

Discussion

Septo-optic dysplasia was originally described by de Morsier[1] as a pathologically distinct entity characterized by an absent or hypoplastic septum pellucidum, a primitive optic vesicle, and dysplasia of the optic nerve, chiasm, and optic tracts. Since then, it has been recognized that septo-optic dysplasia actually represents a spectrum of midline developmental anomalies that include optic nerve hypoplasia and possible pituitary insufficiency.

Clinically, septo-optic dysplasia can be manifested in several different ways. Blindness of those afflicted will often prompt the caregivers to seek medical attention for them. Depending on the severity of the optic nerve hypoplasia, patients can have no pupillary light responses, roving or searching ocular movements, nystagmus, and strabismus.[5] Although most patients

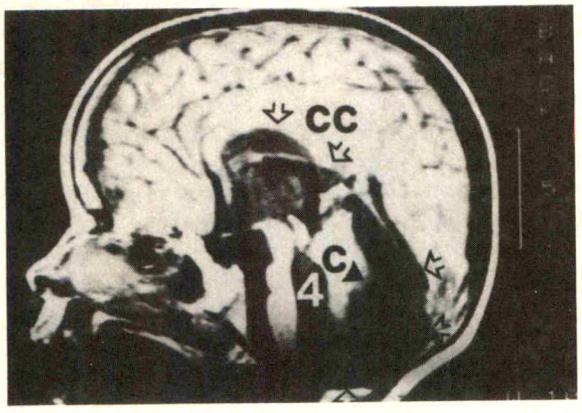

Fig. 4 (Benner and associates). Patient 1. Sagittal magnetic resonance image shows partial agenesis of the splenium and posterior body of the corpus callosum (CC between open arrows). The open arrows outline a large posterior fossa cyst connecting with the fourth ventricle through a defect in the vermis. The cerebellum (C, solid arrow) is hypoplastic.

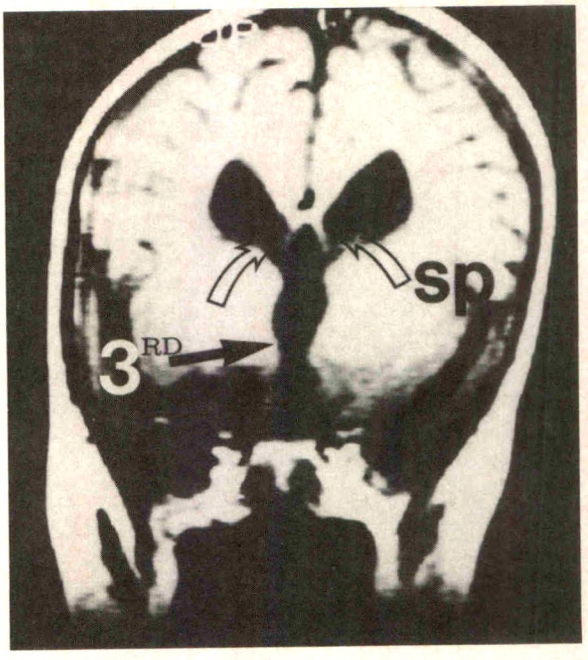

Fig. 5 (Benner and associates). Patient 2. Coronal magnetic resonance image shows laterally deviated leaves of the septi pellucidi (SP) connecting the hypoplastic corpus callosum to each of the separated fornices. The third ventricle is dilated and elevated and the lateral ventricles show enlarged occipital horns of the lateral ventricles.

have marked visual impairment, the visual acuity can range from near normal (20/30) to no light perception.[5] The hallmark of optic nerve hypoplasia, as seen ophthalmoscopically, is a small disk one third to one half of the normal size surrounded by an inner yellow ring and an outer pigmented ring, which compose the "double ring" sign[4] (Fig. 1).

Patient 1 had both hypothyroidism and no growth hormone response to an arginine and L-dopa challenge. Patient 2 had a cessation of linear growth, suggesting a growth hormone deficiency, but this could not be verified because further testing was refused. Since the initial association of hypopituitarism with septo-optic dysplasia by Hoyt and associates,[2] it has become apparent that as many as two thirds of these patients will have some form of pituitary insufficiency.[6] A review of published reports disclosed 177 cases of septo-optic dysplasia where the patient's pituitary status was detailed; 109 (62%) patients had decreased pituitary function. Affected infants during the neonatal period may have hypoglycemia not associated with hyperinsulinemia, prolonged neonatal jaundice, apnea, or seizures.[6,7] Involvement of the hypothalamic system or pituitary system or both varies from an isolated deficiency of growth hormone to panhypopituitarism. Arslanian and associates[8] demonstrated that the most common pituitary abnormality was a deficiency of growth hormone, which was seen in 73% of patients. These patients typically show a deceleration of linear growth below the fifth percentile for age. However, normal growth in the absence of growth hormone has been documented, possibly mediated by prolactin.[6] Of the patients with a growth hormone deficiency, 50% also had other hormonal deficiencies. The next most common abnormality was a deficiency of adrenocorticotropic hormone seen in 34% of patients, followed by antidiuretic hormone with diabetes insipidus in 26% of patients, and thyroid-stimulating hormone in 21% of patients.[8]

In addition to their pituitary abnormalities, both siblings had additional neurologic impairments, including seizures that were refractory to medical therapy and profound delays in their psychomotor development. A review of published reports disclosed 48 cases with a description of the patient's neurologic status. Of these 48 patients, 20 (42%) had one or more of the nonpituitary neurologic deficits described. Seizure disorders were the most commonly reported abnormalities (ten patients [50%]), followed by delays in psychomotor development or men-

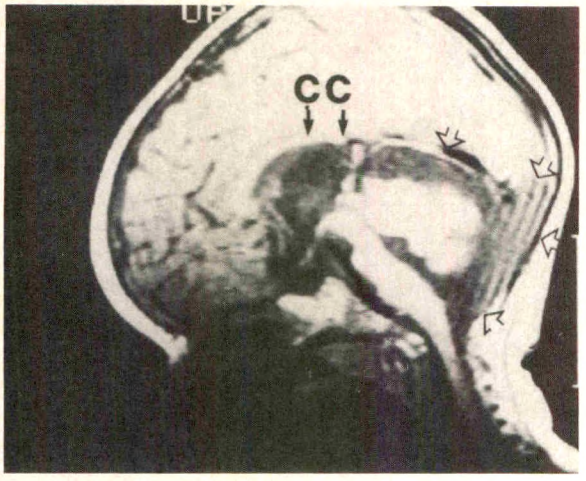

Fig. 6 (Benner and associates). Patient 2. Sagittal magnetic resonance image. The posterior body and splenium of the corpus callosum are hypoplastic (CC between solid arrows). A large posterior fossa cyst (open arrows) connects with the fourth ventricle through an area of partial agenesis of the cerebellar vermis.

tal retardation (eight patients [40%]), and hemiparesis (three patients [15%]).

The neurologic deficits seen in the siblings we studied are not surprising when one considers the extensive midline brain anomalies discovered with neuroradiologic imaging. Each of the siblings had partial agenesis of the corpus callosum, a dilated third ventricle, lateral splitting of the leaves of the septum pellucidum, and partial agenesis of the cerebellar vermis. A review of published reports disclosed three cases of septo-optic dysplasia associated with agenesis of the corpus callosum.[9,10] None of these patients had seizures or any additional neurologic defect except for their visual impairment and hypopituitarism. This association may be seen more frequently in future cases as more patients are studied with magnetic resonance imaging. Because of its ability to obtain direct sagittal images and its excellent definition of white matter anomalies, magnetic resonance imaging is the neuroradiologic study of choice for imaging midline cerebral malformations.[10]

The posterior fossa abnormalities seen in our patients are consistent with a variant of the Dandy-Walker syndrome. This syndrome is characterized by aplasia or hypoplasia of the cerebellar vermis, cystic dilatation of the fourth ventricle, and a posterior fossa cyst.[11] Dandy-Walker has been associated with agenesis of the corpus callosum and other midline cerebral malformations.[11-15]

Embryologically, the abnormal neural structures seen in these patients could all result from an insult at approximately six weeks' gestation. In optic nerve hypoplasia, there is an absence or a decreased number of the retinal ganglion cells, which begin to form at six weeks.[16] At the same time, differentiation of the anterior telencephalic wall occurs, creating a cellular thickening referred to as the lamina reuniens. This thick anterior wall of the telencephalon leads to the development of the corpus callosum, septum pellucidum, fornix, and the septal nuclei of the anterior hypothalamus. In the hindbrain, the two rhombic lips of the rhombencephalon grow together by about six weeks and form the vermis and remainder of the cerebellum.[17] Theoretically, a global insult at about six weeks of gestation or earlier could have been responsible for all of the neural abnormalities that developed in our patients. Despite an extensive work-up, we were unable to identify a specific causative teratogen, chromosomal abnormality, or metabolic imbalance that could have caused such a global insult. The only common element between the two siblings is their parentage and genetic pools. One could speculate that an autosomally recessive defect was passed on by two heterozygous parents, or a dominant germinal mutation occurred in a parent's genome. This hypothetical genetic error could have led to faulty neural embryogenesis.

According to de Morsier, septo-optic dysplasia denoted a specific pathologic entity that described the association between optic nerve hypoplasia and the absence of the septum pellucidum.[1]

With time, it has become apparent that the presence or absence of a septum pellucidum is not critical in septo-optic dysplasia. Only 96 of the 187 patients described in published reports (51%) had no septum pellucidum. Perhaps the term septo-optic dysplasia has become a misnomer in that it overemphasizes the septum pellucidum and does not include a spectrum of midline central nervous system anomalies that are related developmentally. Nonetheless, septo-optic dysplasia remains a valuable clinical syndrome because it links a specific group of ocular anomalies with a potentially treatable and often unsuspected hypothalamic insufficiency or pituitary insufficiency or both.

The familial occurrence of this disorder raises

the possibility of autosomal-recessive inheritance. Ophthalmologists, pediatricians, and geneticists must be aware of the possibility of familial occurrence of septo-optic dysplasia and the need for appropriate family counseling.

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OPHTHALMIC MINIATURE

She seemed to have a habit, when saying melodramatic things like that, of widening her blue eyes to full moons. It produced such a soulful look of sincerity that it automatically made me doubt that sincerity. In addition, it's very difficult to reply without stuttering to somebody who looks at you like that.

Nancy Pickard, *Dead Crazy*
New York, Pocket Books, 1988, p. 3

Observations Concerning Patients With Suspected Impending Macular Holes

J. Donald M. Gass, M.D., and Brian C. Joondeph, M.D.

Between September 1987 and April 1989, 18 patients (21 eyes) with suspected impending Stage 1 macular holes were referred to the Bascom Palmer Eye Institute. Only one patient had a Stage 1 hole. The others had an aborted stage of macular hole formation (eight eyes), Stage 2 holes (four eyes), a Stage 3 hole (one eye), or other lesions unrelated to hole formation. We believed that most of the apparently incorrect referring diagnoses were the product of incorrect interpretation of the biomicroscopic and fluorescein angiographic findings, and were not caused by changes occurring before our examination.

A BIOMICROSCOPIC CLASSIFICATION of the stages of development of an idiopathic senile macular hole has been established.[1,2] The primary mechanism of hole formation was postulated to be spontaneous, usually abrupt, focal contraction of the prefoveal vitreous cortex, which elevates the retina in the foveolar area (Stage 1 traction-al detachment or impending macular hole). Further contraction causes a tangential tear, usually at one edge of the fovea (Stage 2 hole). Over several months or longer, the tear enlarges to a fully developed one-third disk-diameter–sized hole (Stage 3). The focal vitreous contraction is accompanied by blurring and metamorphopsia and produces a characteristic biomicroscopic appearance of a yellow spot (Stage 1A) or ring (Stage 1B) and loss of the foveolar depression in the absence of evidence of posterior vitreous detachment. Xanthophyll is highly concentrated in the floor of the fovea (foveola), and its greater visibility as the retina detaches is probably the cause of the yellow spot, which changes to a larger ring configuration as the retinal detachment increases and the foveolar retina becomes more attenuated.[1,2]

Progression from Stage 1 to Stage 2 usually occurs between one week and several months. In approximately 50% of the affected patients, however, this process is aborted as spontaneous vitreofoveal separation occurs and visual acuity improves to levels of 20/20 to 20/40. In some of these patients, a focal condensation of vitreous cortex is visible biomicroscopically as an oscillating structure (pseudo-operculum) immediately in front of the reattached fovea. In other patients, the tangential force of focal vitreous contraction strips off the inner retinal tissue to create an inner lamellar, red, retinal hole, often with an overlying operculum. Because approximately 50% of the eyes with Stage 1 impending holes progress to Stage 3 holes and visual loss (usually in the range of 20/70 to 20/200), a multicenter randomized controlled clinical trial was recommended to determine the efficacy of surgical peeling of the vitreous cortex in preventing hole formation. Serge de Bustros, M.D., of the Wilmer Ophthalmological Institute, initiated such a trial, and as a result increasing numbers of patients have been referred to the Bascom Palmer Eye Institute because of suspected Stage 1 holes. Most of these patients, however, have had lesions mistaken for Stage 1 holes. We describe herein the biomicroscopic and fluorescein angiographic features of a Stage 1 hole, and those lesions that may be mistaken for it.

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Subjects and Methods

Between Sept. 15, 1987, and April 15, 1989, 83 patients with various stages of idiopathic macular holes were referred to the Bascom Palmer Eye Institute. Of these patients, 18 (21 eyes) had suspected impending Stage 1 holes. All patients had a complete ocular examination by one of us (J. D. M. G.), including contact lens evaluation of the fundi. Most patients underwent fluorescein angiography.

Results

Of the 18 patients referred for possible vitrectomy, only one had a Stage 1 hole (Fig. 1). There were many causes for visual symptoms in the 17 patients (20 eyes) who did not have Stage 1 holes (Figs. 2 to 8). In five eyes, there were sharply demarcated, red, inner lamellar holes of various sizes and shapes (Fig. 2, middle, and Fig. 3). In one patient, who complained of a small, yellow paracentral scotoma, an operculum lying immediately in front of the lamellar hole on the back surface of the partly detached hyaloid membrane cast a yellow shadow on the retina adjacent to the lamellar hole as the slit-beam was moved from side to side. Four eyes showed posterior vitreous detachment from the optic disk and macula. Visual acuities were 20/20, 20/25, 20/25, 20/40, and 20/50, respectively.

Four eyes had Stage 2 holes with a small rim of surrounding retinal detachment and fine radiating retinal folds (Fig. 4, middle, and Fig. 5). One eye had a posterior vitreous detachment and three did not. One patient had an operculum without a posterior vitreous detachment (Fig. 5). Visual acuities were 20/25, 20/25, 20/60, and 20/60, respectively. One patient with visual acuity of 20/40 had a Stage 3 hole.

Three eyes had vitreofoveal separation and a pseudo-operculum oscillating in front of the fovea (Fig. 2, top). Visual acuities were 20/20, 20/20, and 20/30, respectively. Two of the patients were aware of a small, paracentral moving scotoma in the affected eye.

In six eyes, an epiretinal membrane was responsible for the misdiagnosis of Stage 1 holes. In each of four eyes there was a hole in the epiretinal membrane in the foveolar area (Fig. 7, left, and Fig. 8, top left). Visual acuities were 20/20, 20/25, 20/25, and 20/50, respectively. In two eyes, the epiretinal membrane bridged the foveolar area, and in one it was associated with a central yellow spot (Fig. 7, left). Visual

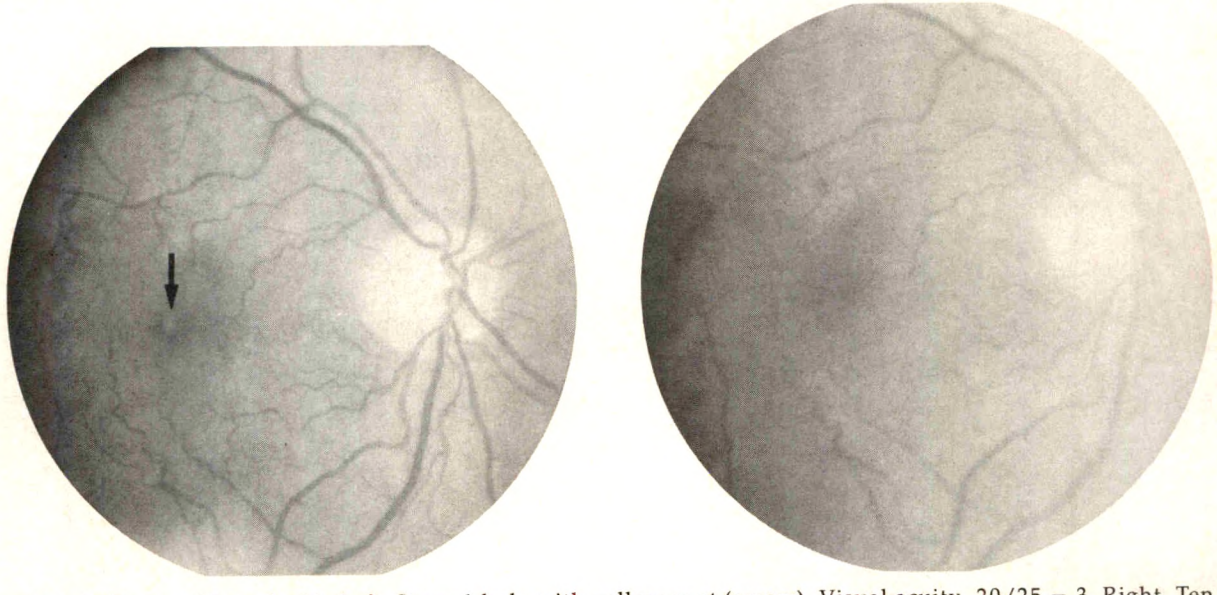

Fig. 1 (Gass and Joondeph). Left, Stage 1 hole with yellow spot (arrow). Visual acuity, 20/25 − 3. Right, Ten months later. Spontaneous vitreofoveal detachment with pseudo-operculum (not visible in photograph). Visual acuity, 20/20. Note spot in foveola is gone.

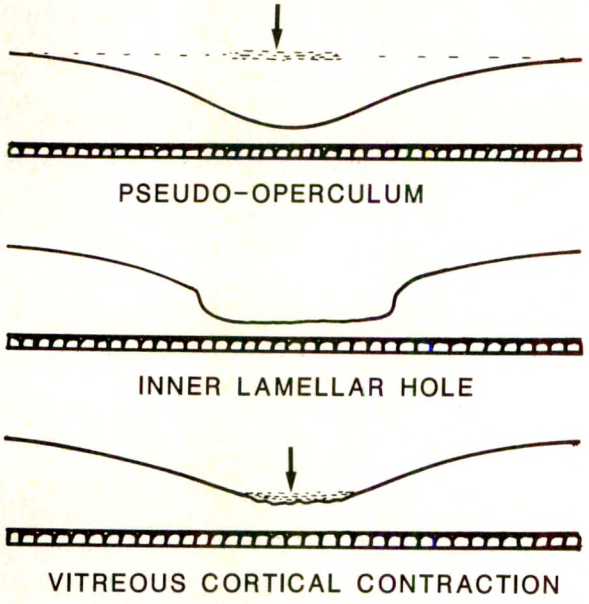

Fig. 2 (Gass and Joondeph). Aborted stages of macular hole mistaken for Stage 1 holes. Top, Pseudo-operculum (arrow). Middle, Inner lamellar hole (see Fig. 3). Bottom, Vitreous cortical contraction (arrow) without hole formation (see Fig. 8, middle right).

acuities were 20/25 and 20/40. Neither eye had posterior vitreous detachment.

One patient with visual acuity of 20/30 had a single yellow druse or foveal thinning of the pigment epithelium and no loss of the foveal depression.

In one eye with visual acuity of 20/20, a translucent slightly yellow ring-shaped structure was visible on the inner retinal surface at the margin of the foveola unassociated with loss of the foveal depression (Fig. 7, left, and Fig. 8, top right). There was no vitreous separation from the optic disk, but there was evidence that it was separated from the macular area.

Discussion

Our finding that 13 of 21 eyes of patients referred because of Stage 1 holes had Stage 2 holes (four eyes), a Stage 3 hole (one eye), or one of the aborted stages of macular hole formation (eight eyes) suggests that either there was a delay in referral or biomicroscopic findings were misinterpreted by the referring physician. We believe that in most instances findings were misinterpreted by the referring physician. Our experience before 1987 suggested that inner lamellar holes and pseudo-opercula were frequent causes of misdiagnoses of an impending hole usually in the fellow eye of a patient with a macular hole in one eye.[2]

A yellow spot or ring, loss of the foveal depression, and absence of evidence of vitreous separation from the optic disk (papillary vitreous condensation ring) and the fovea (pseudo-operculum) are the cardinal biomicroscopic signs of an impending Stage 1 macular hole.[2] These signs are nearly always associated with

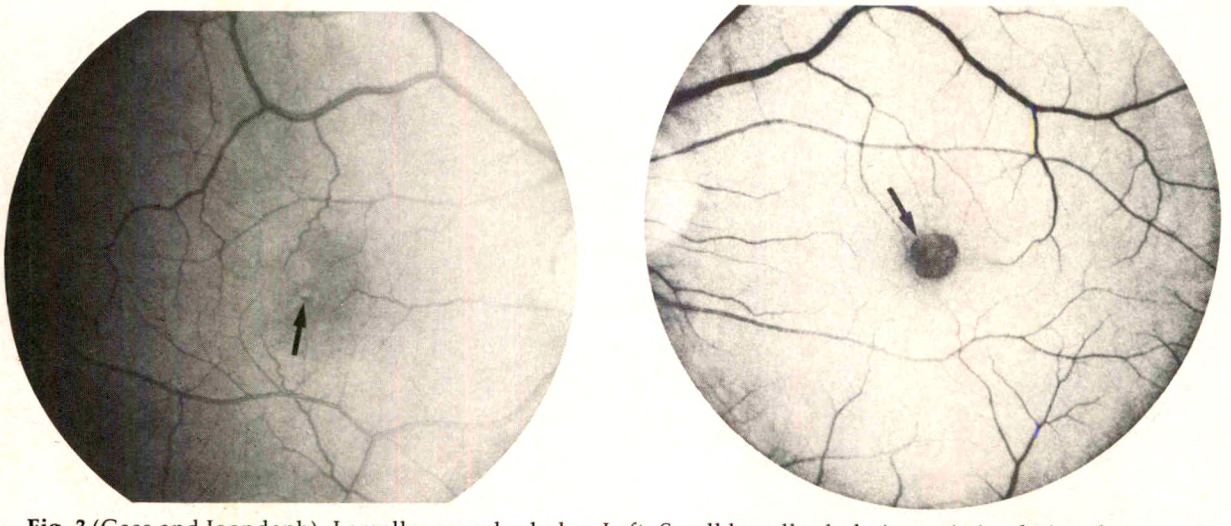

Fig. 3 (Gass and Joondeph). Lamellar macular holes. Left, Small lamellar hole (arrow) simulating that seen in sungazing. Visual acuity was 20/20. Right, Large, slightly irregular lamellar hole (arrow). Visual acuity was 20/25. Results of angiography were normal.

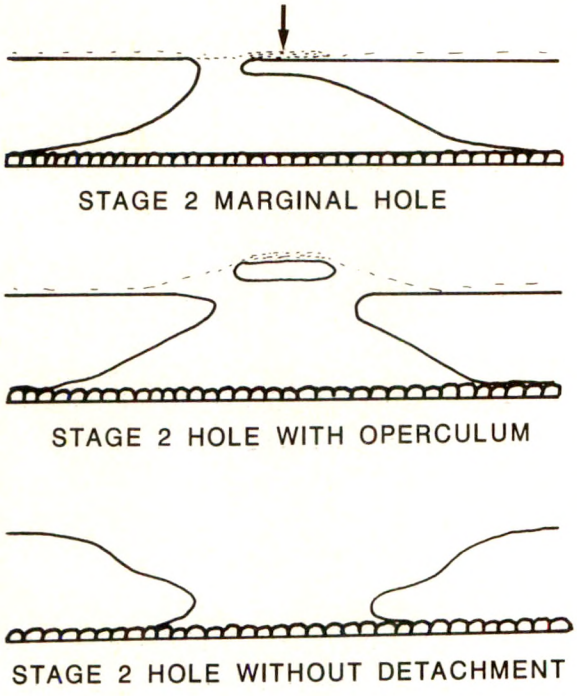

Fig. 4 (Gass and Joondeph). Stage 2 holes mistaken for Stage 1 holes. Top, Contracted vitreous cortex (arrow) causing early marginal hole. Middle, Hole with an operculum that is almost as large as the hole (see Fig. 6, left). Bottom, Hole without surrounding retinal detachment (see Fig. 7).

mild loss of visual acuity and metamorphopsia. In some patients, the detached foveolar retina is sufficiently attenuated and the amount of xanthophyll is so low that the central lesion has the appearance of a red cyst. In such cases, if the area of detachment is greater than one-half disk diameter, a Stage 1 hole may simulate either a Stage 2 or Stage 3 hole biomicroscopically, because the separated thick perifoveolar retina appears as a halo surrounding the sharply delineated central area of attenuated foveolar retina that may be visible only with a thin slit-beam of light. Spontaneous vitreofoveal separation occurring in such cases probably accounts for some of the reported cases of disappearing macular holes.[3] Focal hyperfluorescence may be evident within the central area of the foveal detachment because of increased transmission of choroidal fluorescence attributable to attenuation of the foveolar retina and xanthophyll. If spontaneous vitreoretinal separation and foveal reattachment without full-thickness hole formation occurs, the fluorescence may be no longer evident.[2]

Biomicroscopic features of an inner lamellar hole that should readily distinguish it from a Stage 1 hole include the following: evidence of vitreofoveal separation often accompanied by an operculum; presence of a foveal depression; and one (or occasionally multiple) sharply circumscribed round, oval, or petal-shaped, red

Fig. 5 (Gass and Joondeph). Left, Stage 2 hole simulating Stage 1 hole. Central yellow spot (arrow) is an operculum lying just in front of, and largely obscuring, a full-thickness hole. Note halo of detachment. Compare with Figure 4, middle. Right, Eight months later, the hole has enlarged (Stage 3) and the operculum (arrow) has contracted.

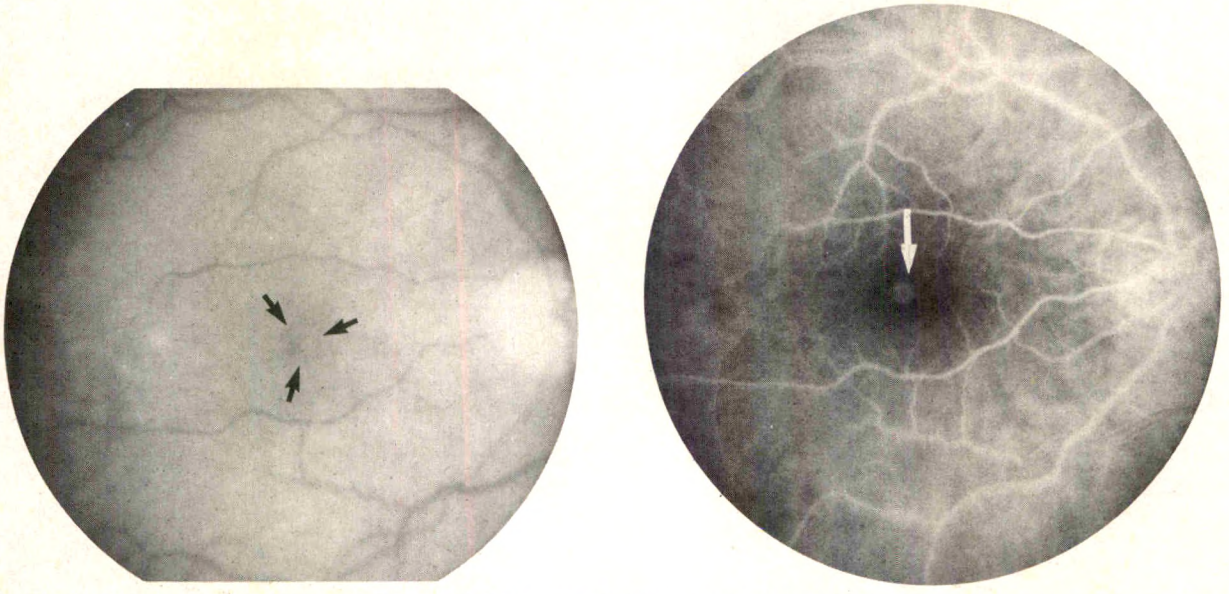

Fig. 6 (Gass and Joondeph). Left, Stage 2 hole (arrows) without retinal detachment simulating a macular cyst or lamellar hole. Visual acuity was 20/25. Compare with Figure 4, bottom. Right, Angiogram shows intense fluorescence (arrow), suggesting Stage 2 hole. Seven months later, there was a fully developed Stage 3 hole with a halo of retinal detachment. Visual acuity was 20/200.

depression in the inner retinal surface (Fig. 3). The contracting focal area of vitreous cortex in these eyes causes one or more irregular breaks in the inner retina as it shrinks centrally. Once vitreofoveal separation occurs, there is no tendency for the appearance of the lamellar defect or the patient's visual acuity to change. Inner lamellar holes may be difficult to distinguish biomicroscopically from a full-thickness hole in those infrequent instances in which spontaneous reattachment of the retina around the full-thickness hole occurs (Fig. 4, bottom, and Fig. 6). Both holes may be associated with near normal visual acuity. If the hole is partial thickness only, the patient usually will see no defect in a thin slit-beam of light and will see a 50-μm spot laser aiming beam light directed toward the hole. Fluorescein angiography in the full-thickness hole usually shows moderately intense early fluorescence in the area of the hole (Fig. 6), whereas it typically shows either no or slight hyperfluorescence in a lamellar hole.

Mild visual complaints and the finding of a small, usually round, less than 100-μm diameter, semitranslucent structure (pseudo-operculum) in front of the foveola may mistakenly suggest to the ophthalmologist that an impending macular hole is present (Fig. 2, top). This is usually discovered in a patient who has a macular hole in the fellow eye. The visual acuity is often near normal. The movement of the pseudo-operculum in front of the otherwise intact foveola may cause the patient to complain of a small moving spot. The presence of a pseudo-operculum is a sign indicating an excellent prognosis.

A sharply defined oval or round hole in an epiretinal fibrocellular membrane in an eye with good visual acuity, usually 20/30 or better, may be misinterpreted either as an impending hole or a Stage 3 hole. The presence of a crinkled reflex from the inner surface surrounding the hole, and the absence of a halo of retinal detachment, operculum, or yellow deposits at the level of the pigment epithelium centrally are the distinguishing features of a hole in an epiretinal membrane (Fig. 7, left, and Fig. 8, top left).[4] A posterior vitreous detachment may or may not be present. The appearance of these epiretinal membranes and the patient's visual acuity usually do not change. Additional contraction or growth of these membranes may occasionally cause more retinal distortion. In some patients, their spontaneous peeling from

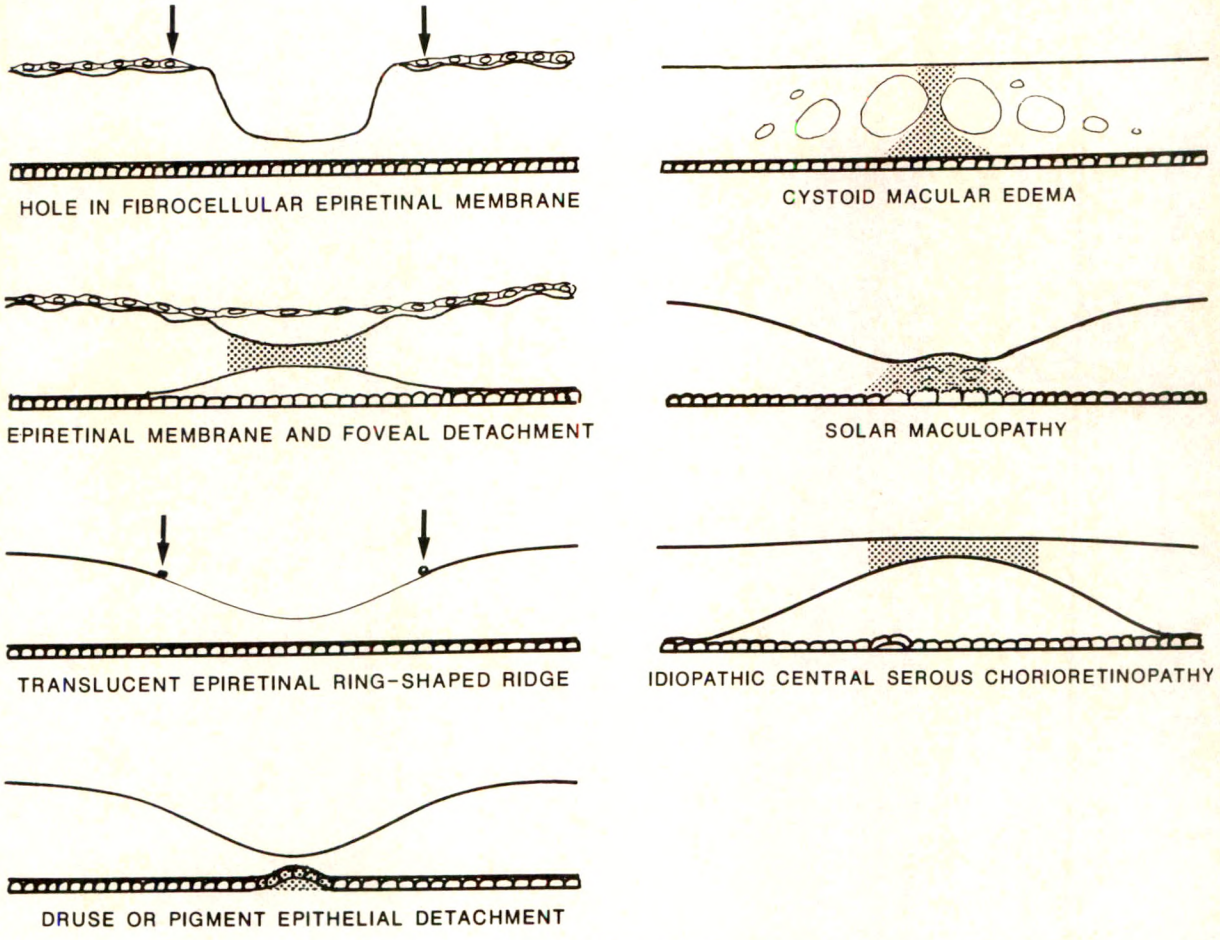

Fig. 7 (Gass and Joondeph). Other disorders mistaken for Stage 1 hole. Left panel, Hole in contracted fibrocellular epiretinal membrane (arrows) (see Fig. 8, top left); central fibrocellular epiretinal membrane with macular detachment; translucent circular ridge (arrows) on inner retinal surface (see Fig. 8, top right); and central druse or retinal pigment epithelium elevation. Right panel, Cystoid macular edema (see Fig. 8, middle left); solar maculopathy (see Fig. 8, bottom left); and foveal detachment caused by idiopathic central serous retinopathy (see Fig. 8, bottom right). Stippling indicates yellow color evident biomicroscopically.

the retinal surface may result in less distortion and visual improvement.

We are uncertain about the nature of the translucent epiretinal ring-shaped ridge surrounding the foveolar area seen in one patient (Fig. 7, left, and Fig. 8, top right). It may represent a condensed ring of vitreous cortex at the site of a dehiscence in the cortex that occurred during vitreofoveal separation.

The yellow spot noted in one of our patients with an epiretinal fibrocellular membrane bridging the macula was probably caused by an underlying foveal detachment produced by the membrane (Fig. 7, left). Because the membrane spans the entire macular area, the risk of its causing a macular hole is low.

The differentiation between an impending Stage 1 hole accompanied by a yellow ring and early Stage 2 hole may be difficult. The use of a thin slit-beam of light to identify the presence or absence of a transparent membrane bridging the area of the yellow ring is the most important method to differentiate the two holes. If a membrane is evident, it is probably the attenuated foveolar retina and not the posterior hyaloid,

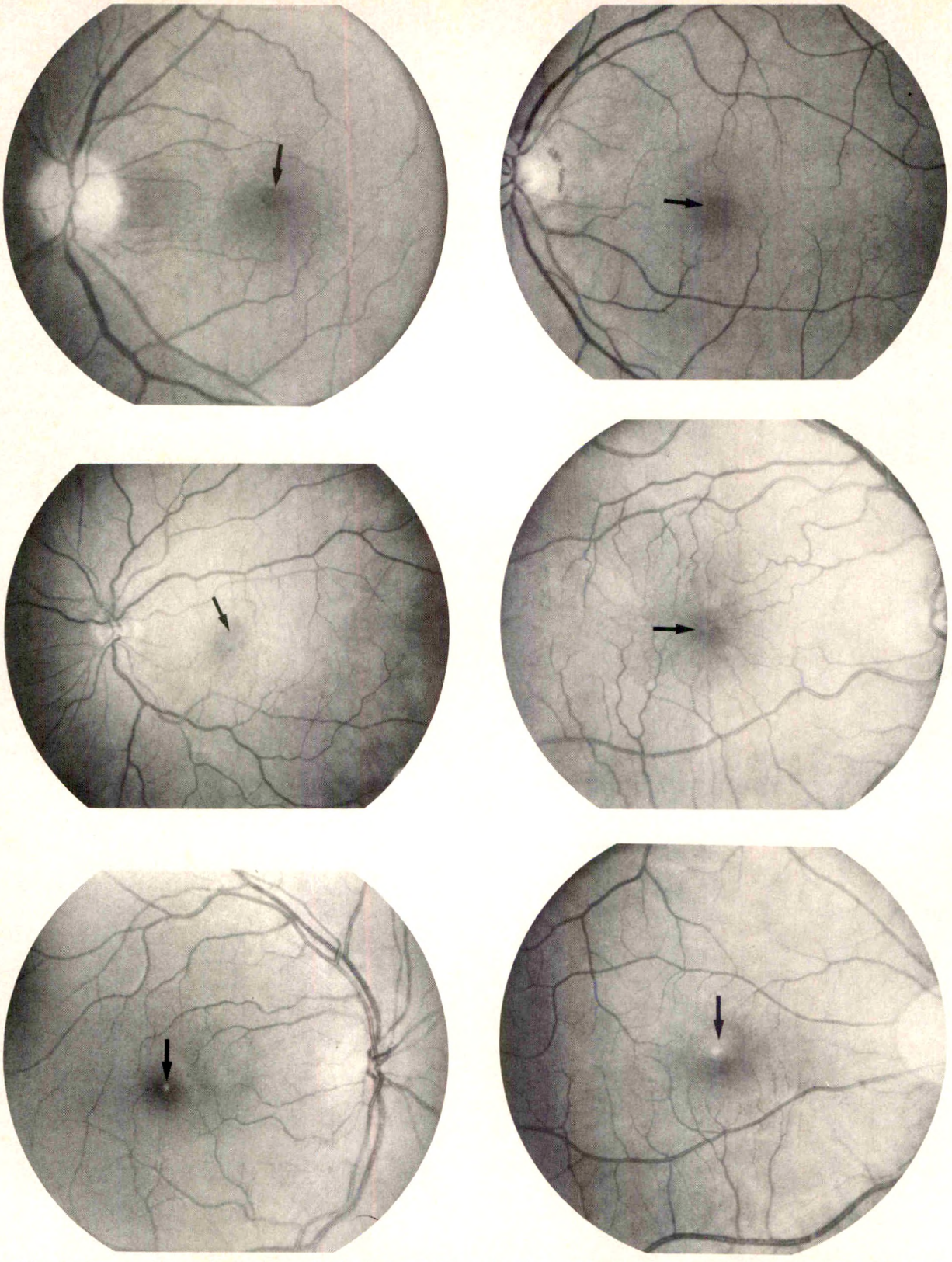

Fig. 8 (Gass and Joondeph). Macular lesions mistaken for Stage 1 hole. Top left, Hole (arrow) in epiretinal membrane. Visual acuity was 20/20 (see Fig. 7, left). Top right, Translucent epiretinal ring-shaped ridge (arrow). Visual acuity was 20/20 J-1 (see Fig. 7, left). There was no change one year later. Middle left, Yellow spot (arrow) caused by cystoid macular edema with epiretinal membrane. Visual acuity was 20/30. Angiography showed marked cystoid edema (see Fig. 7, right). Middle right, Vitreous cortical contraction causing stellate epiretinal yellow lesion (arrow) and radial retinal folds but no hole formation. Visual acuity was 20/25. This was unchanged three years later. Bottom left, Yellow spot (arrow) caused by sungazing. Visual acuity was 20/50 (see Fig. 7, right). Bottom right, Yellow spot (arrows) and foveal detachment in a patient with idiopathic central serous chorioretinopathy. Visual acuity was 20/25. Angiography showed paracentral focal leak (see Fig. 7, right).

which cannot be detected biomicroscopically when it bridges a large, full-thickness Stage 3 macular hole and supports an operculum suspended within the area of the hole. In most eyes, the first sign of a hole manifests as a small oval or crescent-shaped red dehiscence at one margin of the detached foveolar retina at the inner edge of the yellow ring. The presence of early, uniform mild fluorescence within the area of the yellow ring is unreliable in distinguishing a Stage 1 from an early Stage 2 hole. If the fluorescence is intense, it is more suggestive of the presence of a hole.

Either a focal area of pigment epithelial depigmentation or a druse was the cause of a yellow spot and misdiagnosis in one patient with good visual acuity and no loss of foveal depression (Fig. 7, left). Drusen are occasionally present in the fellow asymptomatic eye of patients with a macular hole in the one eye, but appear to be a coincidental finding in these patients whose average age is 65 years when they develop a macular hole. A centrally located druse, if associated with a small amount of subretinal fluid, might cause symptoms and biomicroscopic findings indistinguishable from a Stage 1 hole.

With the development of cystoid macular edema, either in aphakic eyes or from other causes, a central yellow spot in the outer part of the swollen polycystic retina is often evident (Fig. 7, right, and Fig. 8, middle left). The yellow color is probably caused by a central compression of the foveolar xanthophyll by the surrounding extracellular fluid, particularly that in Henle's layer.[1] Cystoid macular edema, probably caused by a focal venular occlusion, was responsible for the yellow spot, loss of the foveal depression, mild epiretinal membrane changes, and a misdiagnosis of an impending macular hole in one patient (Fig. 8, middle left).

There are three other lesions that may simulate a Stage 1 hole, although none were the cause of misdiagnosis during the time of this study. One of these appears to be the result of an aborted attempt at hole formation. In these patients, the focus of contracted prefoveolar cortex fails to cause a dehiscence of the retina but remains attached to the inner surface of the foveal center as a stellate, yellow plaque causing a radiating pattern of fine tractional retinal folds, which simulates that seen in foveal retinoschisis (Fig. 2, bottom, and Fig. 8, middle right). Retinal detachment confined to the foveolar area from any cause, including Stage 1 impending hole, usually causes a yellow spot (Fig. 7, right, and Fig. 8, bottom right). It is seen clinically most often in middle-aged men with the early development of idiopathic central serous choroidopathy. The yellow spot may become less apparent as the area of retinal detachment enlarges. Angiography shows evidence of focal staining in the area of the detachment. The yellow spot that is present biomicroscopically and angiographically for several days or weeks after sun gazing may appear identical to that of a Stage 1 hole. The yellow color is presumably caused by greater visibility of the xanthophyll induced by the photochemical and structural alterations of the foveolar retina.

It was partly because of the difficulty in distinguishing Stage 1 holes from many other disorders associated with a yellow foveal spot or ring that only fellow eyes of patients with a macular hole in the one eye were included in the randomized clinical trial for the treatment of Stage 1 holes. We believe the rate of correct diagnoses will improve with further dissemination of information about the biomicroscopic findings of an impending Stage 1 hole and lesions that simulate it. Although our experience suggests that the opportunity for seeing patients with Stage 1 holes is infrequent and that recruitment will require the cooperation of many physicians and ophthalmology centers, we believe that the recently organized randomized trial to determine the effectiveness of vitrectomy in preserving central acuity should continue. The evidence to date suggests that at least 50% of Stage 1 holes will progress to fully developed holes and visual acuity ranging from 20/70 to 20/400.[2] Although a pilot study has demonstrated the feasibility of vitreous peeling in such cases,[5] a randomized controlled clinical trial is necessary to determine its value.

In patients with fully developed Stage 3 or Stage 4 holes, the average diameter of the holes is 400 to 500 μm, and the diameter of the area of retinal detachment is approximately 1,200 to 1,500 μm. The number of retinal receptor elements in the area of detachment is approximately seven times that in the area of the hole. Preservation of the cones in this area by early reattachment offers the possibility of achieving visual acuity in the range of 20/25 to 20/40.

Because the physicians participating in the clinical trial will have opportunity to see many

patients who have early Stage 2 holes, we recommend that these physicians do a pilot study to determine the feasibility of vitreous cortical peeling, intravitreal gas, and small spot size laser in preserving central vision in these patients. Gas injection and patient repositioning alone probably will not be adequate to maintain retinal reattachment because of ingrowth of retinal astrocytes around the edge of the hole onto the inner retina, which in effect produces an ectropion of the hole edges. We have seen enlargement of macular holes and increase in the diameter of retinal detachment after spontaneous separation of the vitreous, and Ron Michels, M.D. (oral communication, May 10, 1987), has seen the same in patients after surgical peeling of the vitreous cortex in eyes with Stage 1 holes.

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OPHTHALMIC MINIATURE

The lack of an E was frustrating, and the asterisks—inserted for the benefit of the typesetter—dazzled his eyes. Between paragraphs, moreover, a pair of piercing eyes kept boring into his consciousness. He knew that kind of stare. It indicated one of two things. The elegant Miss Duckworth was either myopic—or frightened.

Lilian Jackson Braun, *The Cat Who Turned On and Off*
New York, Jove Books, 1986, p. 44

Comparison of Xenon Arc and Argon Laser Photocoagulation in the Treatment of Choroidal Melanomas

Jerry A. Shields, M.D., Lou C. Glazer, M.D., William F. Mieler, M.D., Carol L. Shields, M.D., and Mark S. Gottlieb, Ph.D.

We analyzed the follow-up data in 38 consecutive patients with selected choroidal melanomas that were treated by photocoagulation between 1971 and 1980. Indications for treatment included photographic documentation of tumor growth or an unequivocally positive radioactive phosphorus uptake test, or both. Xenon arc photocoagulation was used in 22 patients (58%) and argon laser was used in 16 patients (42%). At the time of data analysis, the length of follow-up was at least 58 months in all patients. Although all treated tumors were initially eradicated according to ophthalmoscopic and fluorescein angiographic criteria, there was subsequent regrowth in three of the 22 patients (14%) treated with xenon photocoagulation and in ten of the 16 patients (64%) treated with argon laser. The recurrences were observed on an average of 71 months after completion of treatment in the xenon-treated group and on an average of 30 months in the argon-treated group. More treatment sessions were required in the argon laser group to achieve tumor control. Complications of vitreous hemorrhage, cystoid macular edema, and retinal detachment were greater in the xenon photocoagulation group.

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From the Ocular Oncology Service, Wills Eye Hospital, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania. This study was supported in part by the Ocular Oncology Fund and the Oncology Research Fund, Wills Eye Hospital; the Eye Tumor Research Foundation, Gladwyne, Pennsylvania; National Eye Institute Core Grant Ay 01931; and an unrestricted grant from Research to Prevent Blindness, Inc.

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ENUCLEATION, RADIATION, local resection, or photocoagulation have been advocated in the management of malignant melanoma of the choroid.[1-3] Most choroidal melanomas today are treated with radiation or enucleation, although photocoagulation remains a viable option in selected cases. Early reports by Meyer-Schwickerath and Vogel[4-8] addressed the effectiveness of xenon arc photocoagulation for choroidal melanoma. Although argon laser is more widely used by ophthalmologists today, little information is available on the role of argon laser photocoagulation in treating choroidal melanomas. We compared xenon arc and argon laser photocoagulation for their effectiveness in destroying posterior uveal melanomas.

Patients and Methods

We reviewed the charts of all patients with choroidal melanomas who were treated with photocoagulation by one of us (J.A.S.) at our institution between 1971 and 1980. The study was designed to compare the results of xenon arc photocoagulation used between 1971 and 1977 and argon laser photocoagulation used between 1976 and 1980. To study patients with relatively long follow-up, patients treated since December 1980 were not included. The initial diagnosis of melanoma was made on the basis of a melanocytic choroidal lesion with either documented growth, signs of activity such as ill-defined orange pigment and subretinal fluid, or an unequivocally positive radioactive phosphorus uptake (^{32}P) test.[9]

The technique of photocoagulation with both the xenon arc and argon laser was similar to that originally proposed by Meyer-Schwickerath.[4,5] The patients treated with

xenon photocoagulation were routinely given retrobulbar anesthesia with lidocaine hydrochloride. In the earlier cases, the Zeiss xenon photocoagulator was used, and later a portable xenon photocoagulator was used. At the initial treatment, heavy confluent burns were used to surround the tumor completely in an attempt to destroy choroidal blood vessels and leave the large retinal vessels intact (Fig. 1, top left and top right). A spot size of approximately 500 μm was used with enough power to produce a distinct yellow burn. The treatment around the tumor was repeated in three to four weeks. In subsequent sessions three to five weeks apart, direct intense treatment was applied to the tumor itself. During treatment directly to the tumor, small breaks in Bruch's membrane often occurred, sometimes liberating pigmented debris into the overlying retina and vitreous cavity. The eventual goal of photocoagulation was a flat, well-defined yellow-white chorioretinal scar (Fig. 1, bottom left) or a scar with a flat central focus of hyperpigmentation (Fig. 2).[1]

With the argon laser technique, only topical proparacaine anesthesia was used. Treatments were done with the Coherent Radiation Argon laser unit and a standard contact lens. The technique of laser application was identical to that used for xenon photocoagulation. Generally, a spot size of 200 to 500 μm, a duration of 0.5 to 1.0 seconds, and a power of 500 to 1,000 mW were used (Fig. 3). With both the xenon

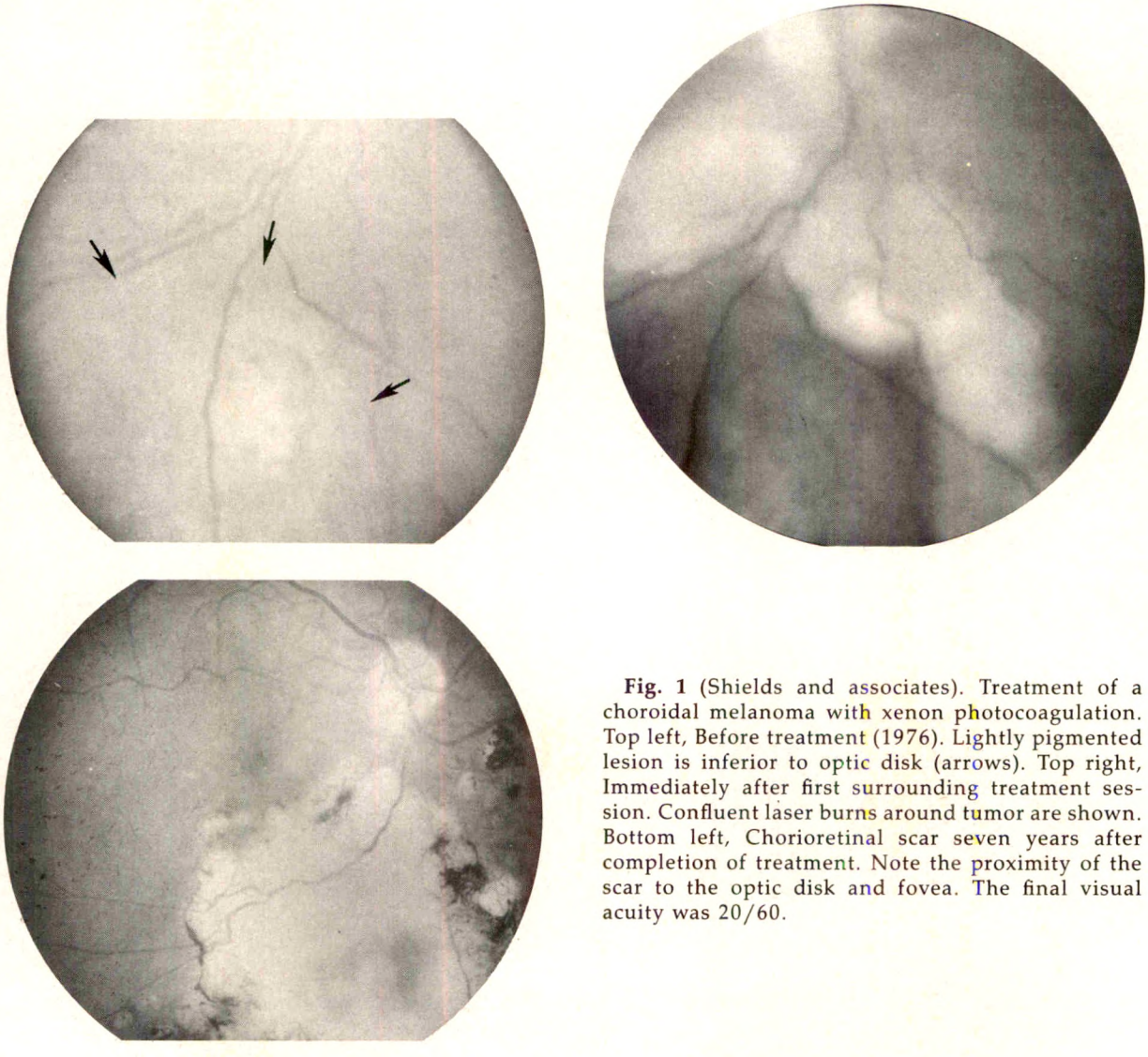

Fig. 1 (Shields and associates). Treatment of a choroidal melanoma with xenon photocoagulation. Top left, Before treatment (1976). Lightly pigmented lesion is inferior to optic disk (arrows). Top right, Immediately after first surrounding treatment session. Confluent laser burns around tumor are shown. Bottom left, Chorioretinal scar seven years after completion of treatment. Note the proximity of the scar to the optic disk and fovea. The final visual acuity was 20/60.

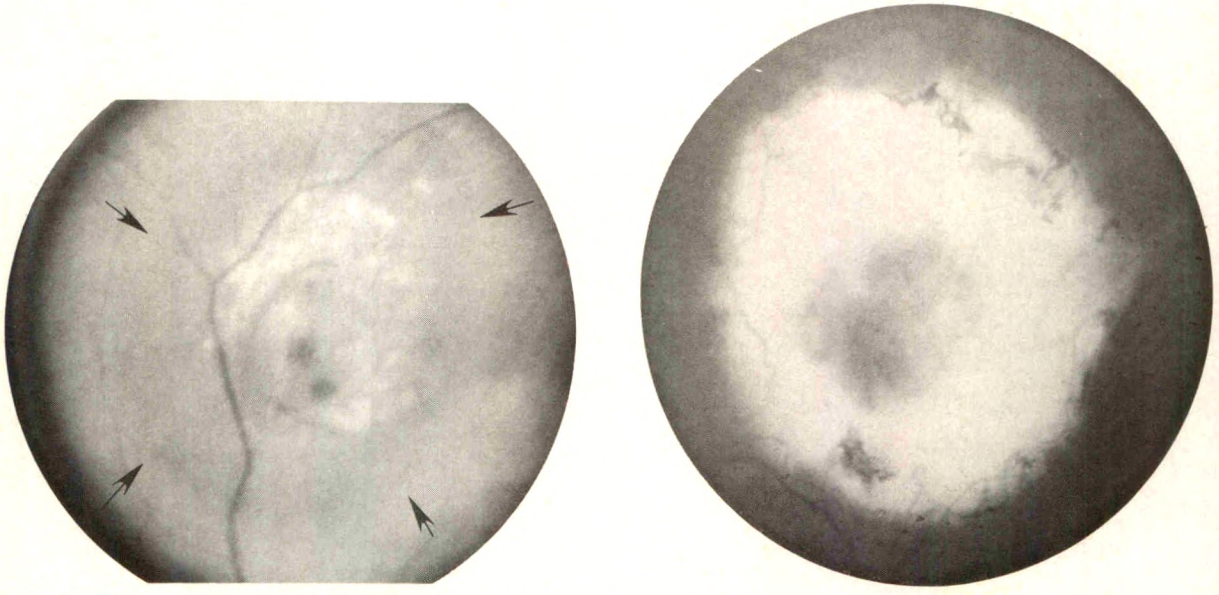

Fig. 2 (Shields and associates). Left, Choroidal melanoma (arrows) between optic disk and equator superiorly. The lesion was treated with xenon photocoagulation. Right, Five years after completion of treatment. Note the flat patch of pigmentation in the center of the treated area.

and argon techniques, treatment was repeated every three to six weeks until the tumor was believed to be clinically eradicated. In cases where the lesion was near the optic disk, it was necessary to destroy all tissue up to the disk margin (Fig. 4).

Usually, follow-up examination was performed in our institution. In a few cases, follow-up was obtained by calling the referring ophthalmologists and obtaining copies of the patient's records, fundus photographs, and fluorescein angiograms.

Data collected included patient age, tumor dimensions, tumor location, type of treatment, number of treatments required per tumor, visual acuity, complications, treatments additional to photocoagulation, duration of follow-up, and mortality.

The difference in effectiveness in the treatment of choroidal melanomas with xenon arc photocoagulation and argon laser was evaluated by the use of survival analysis techniques. Kaplan-Meier estimates of the survival function, with observed tumor growth representing the indicator of treatment failure, were generated for both the xenon arc photocoagulation and argon laser groups and compared by using the life-test procedure. A subsequent analysis to evaluate the potential impact of confounding factors on the comparative treatment effectiveness of the two techniques was performed by using the survival analysis with covariates-Cox models. This analysis generated an adjusted estimate of the ratio of the hazard functions or the relative risk associated with tumor growth vs remission in one treatment group compared to the other.

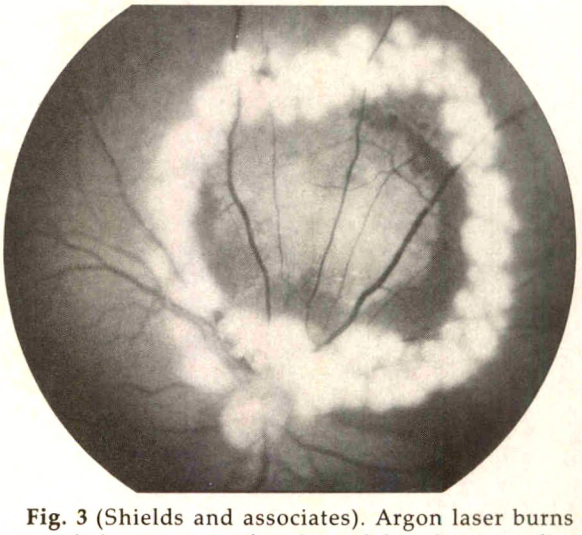

Fig. 3 (Shields and associates). Argon laser burns around the margins of a choroidal melanoma after documentation of growth.

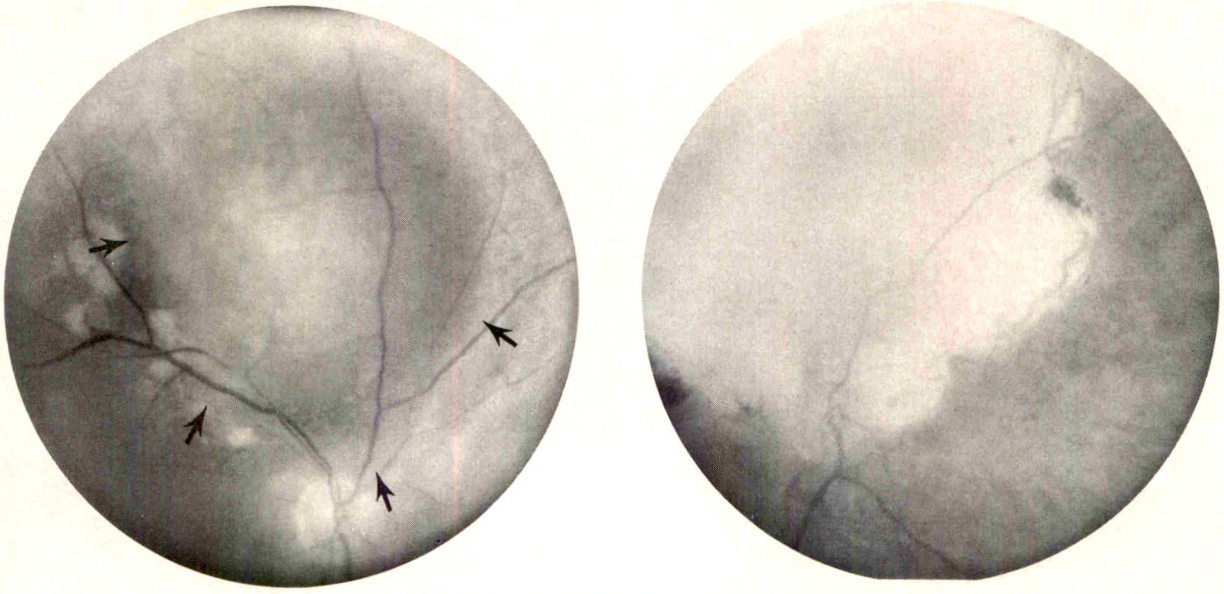

Fig. 4 (Shields and associates). Left, Choroidal melanoma is 3.5 mm thick and located superior to the optic disk. Right, Six years after successful treatment with argon laser photocoagulation. Final visual acuity was 20/60.

Results

Of the 38 patients, 13 were men (34%) and 25 were women (66%). The tumor was located in the right eye in 19 patients and in the left eye in 19 patients.

A comparison of the xenon-treated group and the argon-treated group for general data, tumor data, treatment, and complications is shown in Table 1. Xenon photocoagulation was used in 22 patients (58%), and the argon laser was used in 16 patients (42%). At the time of initiation of treatment, the patients' ages in the xenon group ranged from 33 to 85 years (mean, 60 years), and in the argon group they ranged from 53 to 74 years (mean, 62 years).

The largest tumor diameter ranged from 2.5 to 12.0 mm in the xenon group (mean, 6.5 mm) and from 2.5 to 8.0 mm in the argon group (mean, 6.1 mm). Because most tumors were nearly round, the smallest tumor diameters were almost identical. The tumor thickness as measured by A-scan ultrasonography ranged from 0.5 to 3.0 mm in the xenon group (mean, 2.1 mm) and from 1.0 to 3.8 mm in the argon group (mean, 2.5 mm).

Of the 22 tumors in the xenon group, 15 were greater than 3.0 mm from the foveola and seven were 3.0 mm or less from the foveola. Of the 16 tumors in the argon group, nine were greater than 3.0 mm from the foveola and seven were 3.0 mm or less from the foveola. A serous retinal detachment produced visual loss in six of the patients in the xenon-treated group and in eight of the patients in the argon-treated group.

TABLE 1
CLINICAL DATA ON PATIENTS WITH CHOROIDAL MELANOMA TREATED BY XENON ARC AND ARGON LASER PHOTOCOAGULATION

	XENON	ARGON
No. of patients	22	16
Age range (yrs)	33–85	53–74
Mean patient age (yrs)	60	62
Range of tumor diameter (mm)	2.5–12.0	2.5–8.0
Mean largest tumor diameter (mm)	6.5	6.1
Range of tumor thickness (mm)	0.5–3.0	1.0–3.8
Mean tumor thickness (mm)	2.1	2.5
Distance from foveola		
> 3.0 mm	15	9
< 3.0 mm	7	7
Serous foveal detachment	6	8
No. of treatments		
Range	3–11	4–12
Mean	5	8

TABLE 2
RESULTS OF XENON ARC AND ARGON LASER PHOTOCOAGULATION

	XENON	ARGON
No. of patients	22	16
Range of follow-up (mos)	58–150	58–109
Mean follow-up (mos)	108	77
Successful treatment	19	6
Tumor growth after treatment	3	10
Additional treatment required		
Radioactive plaque	1	1
Enucleation	1	8
Local resection	1	1
Time until tumor regrowth (mos)	7–108	5–57
Mean time until tumor regrowth (mos)	71	30
Deaths	2 (9%)	3 (19%)
Metastatic melanoma	0	2
Other causes	2	1

In the xenon group, between three and 11 treatment sessions (mean, five) were required to achieve tumor destruction. In the argon group, four to 12 treatments (mean, eight) were required.

The range of follow-up after treatment ranged from 58 to 150 months in the xenon group with a mean follow-up of 108 months (Table 2). In the argon group, the follow-up ranged from 58 to 109 months (mean, 77 months). During the follow-up period, the treatment was judged as successful with complete tumor eradication in 19 of the 22 patients (86%) treated with xenon arc and in six of the 16 patients (37%) treated with argon laser. Definite recurrence of the melanoma occurred in three of the 22 xenon-treated patients (14%) and in ten of the 16 argon-treated patients (63%). The difference in treatment failure rate is statistically significant ($P = .004$) by the two-tailed Fisher's exact test.

Of the three tumors that recurred in the xenon-treated group, the recurrence was found in the central portion of the treated area in two patients and on the peripheral margin in one patient. Of the ten tumors that recurred in the argon-treated group, the recurrence was found in the central area in six patients and on the peripheral margin in four patients. The length of time until tumor recurrence ranged from seven to 108 months in the xenon-treated group (mean, 71 months) and from five to 57 months in the argon-treated group (mean, 30 months).

Of the three recurrences in the xenon-treated group, additional treatment included a radioactive plaque in one patient, enucleation in one patient, and local resection of the tumor in one patient. Of the ten recurrences in the argon-treated group, eight patients were treated with enucleation, one patient with a radioactive plaque, and one patient with local resection. The eyes enucleated after tumor recurrence had histologic evidence of viable melanoma cells in the treated area in all instances. We have not yet performed histopathologic studies on eyes of patients in whom the tumor was successfully eradicated on the basis of the clinical criteria described.

Two patients in the xenon-treated group and three patients in the argon-treated group died (Table 2). In the xenon group, both deaths were of causes unrelated to the melanoma. In the argon group, two deaths were attributable to metastatic melanoma and one to an unrelated cause. One of the two melanoma-related deaths occurred in a patient with a family history of malignancy; her mother had died of metastatic choroidal melanoma after enucleation. Both melanoma-related deaths occurred in patients whose choroidal melanoma recurred after photocoagulation, requiring subsequent enucleation of the affected eye.

The complications of the photocoagulation are shown in Table 3. Small focal hemorrhages confined to the treated tumor were not tabulated as complications, because they were present in almost all patients and were of no apparent clinical significance. Cases of visually impairing vitreous or retinal hemorrhage occurred in the two groups. Choroidovitreal neovascularization occurred in four patients in each group. Visually impairing cystoid macular edema and retinal detachment occurred most often in the xenon-treated patients and were not observed in any patient who was noted to have a posterior vitreous detachment before treatment.

TABLE 3
COMPLICATIONS OF PHOTOCOAGULATION FOR CHOROIDAL MELANOMAS

	XENON ARC	ARGON LASER
Vitreous or retinal hemorrhage, or both	6	7
Cystoid macular edema	7	1
Choroidovitreal neovascularization	4	4
Retinal detachment	5	0
Macular pucker	1	0

Excluding the patients who underwent enucleation or who died, the visual results were evaluated for successfully treated tumors that were located 3.0 mm or less from the foveola (Fig. 5, top). Three of the six xenon-treated eyes maintained posttreatment visual acuities of at least 20/60. Two of the three argon-treated eyes maintained similar posttreatment visual acuity. The visual results were also evaluated for successfully treated tumors that were located more than 3.0 mm from the foveola (Fig. 5, bottom). Nine of the 13 xenon-treated eyes maintained visual acuities of 20/60 or better, whereas three of three similar argon-treated tumors maintained this level of visual function.

Because the follow-up time and time from treatment until tumor recurrence were longer in the xenon-treated group, the total time at risk for tumor progression was on the average greater for those tumors in the xenon-treated group. To adjust for the longer follow-up time, and to allow for consideration of possible confounding variables such as tumor size and patient characteristics, a further analysis using Cox's regression model for survival data was performed. This analysis considered the variables in Tables 1 and 2 (with the exception of follow-up time) as covariates to the association of the hazard function for tumor growth or treatment type. Stepwise regression to evaluate these covariates as predictors of the hazard function for tumor growth indicated that only treatmenttype was sufficiently predictive of tumor growth at $P = .002$. The hazard growth risk ratio associated with the use of argon laser was 19.72 times the risk for tumor growth after xenon treatment when the total time at risk for tumor growth after treatment was accounted for.

Discussion

Because of the controversy over the benefits of enucleation for posterior uveal melanomas, there has been increased interest in alternative methods of treatment. Since Meyer-Schwickerath introduced and popularized xenon arc photocoagulation for selected choroidal melanomas,[4,5] the role of this therapeutic modality has been addressed in several studies.[6-8,10-12] Xenon photocoagulation has been most widely used; there have been sporadic reports of using argon and krypton laser, but little useful information is available about these methods of laser treatment.[10-12] Based on the most recent studies, it appears that most ophthalmologists who use photocoagulation to treat choroidal melanomas are currently using the argon laser more frequently than the xenon photocoagulator.

Our xenon- and argon-treated groups were similar in patient age, tumor location, tumor diameter, tumor thickness, and presence and degree of associated retinal detachment (Table 1). A significant difference in tumor recurrence after treatment, however, was detected between the two groups. There were three tumor recurrences among the 22 patients treated with xenon photocoagulation (14%) and ten recurrences among 16 patients treated with argon laser (63%) (Table 2).

There are several possible explanations for the higher incidence of recurrence of choroidal melanoma treated with argon laser. The higher incidence may be related to the penetration of the laser. The blue-green wavelength of argon laser is absorbed mainly by the retinal pigment epithelium. Only a small amount of energy penetrates to the underlying choroidal layer, although this is obviated by the use of multiple treatment sessions with sequential deeper penetration of the laser. The treatment goal of a flat yellow-white scar was eventually reached in all eyes treated with argon laser, although 16 patients (64%) later showed recurrence of the tumor.

A second hypothesis for the increased risk of recurrence with argon laser is that the study groups were not exactly comparable. The mean tumor height was slightly greater in the argon group, although the tumor base was slightly smaller. Additionally, tumors in the argon-treated eyes were located closer to the foveola (seven of 16 tumors were within 3.0 mm of the foveola).

In this nonrandomized study, there may have been other uncontrolled variables that could have influenced the outcome. Xenon photocoagulation was used earlier (1971 to 1977) than the argon laser therapy (1976 to 1980). Presumably, as experience with photocoagulation of melanomas was acquired, the results would have been better and the complications would have decreased. Yet the observed results do not support this supposition, because there was a greater incidence of recurrence in the more recently treated argon group.

A long follow-up period is necessary in any study of choroidal melanoma treatment, because recurrences may occur many years after

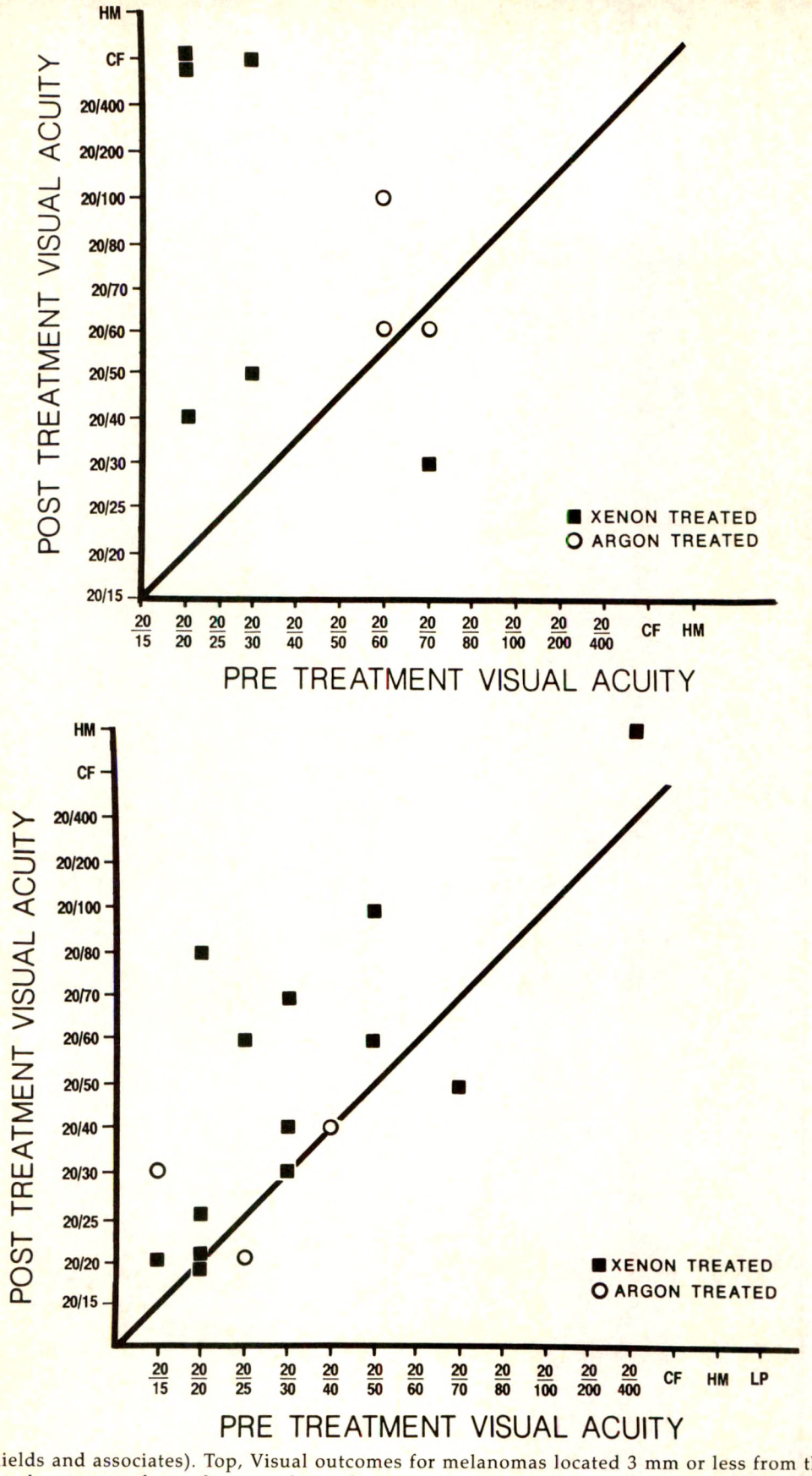

Fig. 5 (Shields and associates). Top, Visual outcomes for melanomas located 3 mm or less from the foveola. Bottom, Visual outcomes for melanomas located greater than 3 mm from the foveola. HM indicates hand motions; CF, counting fingers; and LP, light perception.

therapy. Various investigators have reported recurrences as long as eight years after photocoagulation.[13-15] In this study, the mean follow-up time was 108 months in the xenon group and 77 months in the argon laser group. Although there may be more tumor recurrences in the future, the longer follow-up time in the xenon group would tend to disclose more recurrences in patients treated with this modality. Because there were fewer recurrences in the xenon group, xenon arc photocoagulation may be even more effective when compared to argon laser than indicated by our data.

Seventeen of the 25 (68%) successfully treated tumors (xenon and argon) maintained a final visual acuity better than 20/60. The tumors with a margin within 3.0 mm of the foveola also maintained 20/60 visual acuity or better in five of nine (55%) xenon- and argon-treated eyes (Fig. 5). Overall, the final level of vision was better in the argon-treated group, which was reflected in the greater number of eyes with acute complications after xenon treatment. Unless there were an acute complication at the time of treatment (or eventual tumor recurrence), the eyes generally maintained a stable visual acuity throughout the follow-up period.

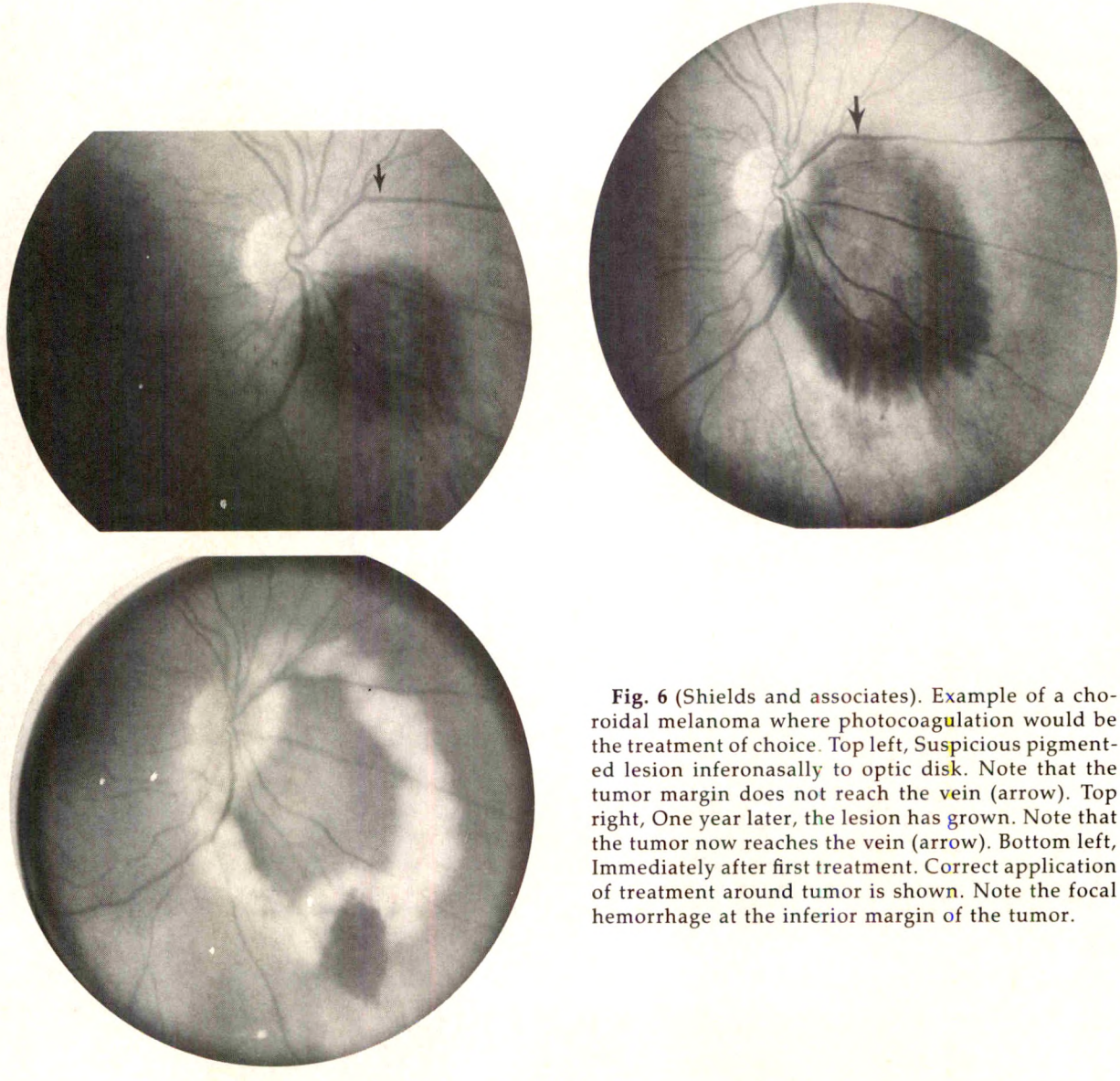

Fig. 6 (Shields and associates). Example of a choroidal melanoma where photocoagulation would be the treatment of choice. Top left, Suspicious pigmented lesion inferonasally to optic disk. Note that the tumor margin does not reach the vein (arrow). Top right, One year later, the lesion has grown. Note that the tumor now reaches the vein (arrow). Bottom left, Immediately after first treatment. Correct application of treatment around tumor is shown. Note the focal hemorrhage at the inferior margin of the tumor.

Photocoagulation is used less frequently at our institution now than it was between 1971 and 1980 because of the recent availability of custom-designed low-energy radioactive plaques. Such plaques can be placed surgically in a posterior location (near the optic disk and fovea) to treat tumors that would have been treated by photocoagulation a few years ago. Furthermore, plaques are ideal for treating small, growing tumors in the equatorial region where photocoagulation would have been our treatment of choice several years ago. Of approximately 300 new patients with choroidal melanomas treated annually at our institution, we use photocoagulation in only two or three instances.

Even though photocoagulation is used less frequently to treat choroidal melanomas today, there are circumstances where it is the treatment of choice. An appropriate case for photocoagulation treatment would be a small choroidal melanoma less than 3.0 mm in thickness located adjacent to the nasal margin of the optic disk, with photographic evidence of growth (Fig. 6). In that location, radiotherapy is more likely to cause optic nerve damage, and the ultimate visual outcome may be better with photocoagulation. Photocoagulation can also be used for any choroidal melanoma less than 3.0 mm in thickness and located at least 3.0 mm from the foveola. However, we currently use radioactive plaques in most such cases. Plaques are less likely to produce immediate hemorrhage and vitreoretinal traction, and the currently used iodine-125 plaques apparently lead to less severe radiation retinopathy than the previously used cobalt-60 plaques.

The results of this study suggest that xenon arc provides better tumor destruction but is associated with a more limited visual outcome, whereas argon laser is less likely to completely destroy the tumor, but when the tumor is adequately treated, it provides a better visual outcome. Further work will be necessary to determine whether other types of lasers will offer further advantages in the treatment of selected patients with choroidal melanomas.

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Bilateral Choroidal Osteoma in Three Siblings

Kenneth G. Noble, M.D.

Three siblings (a sister and two identical-twin brothers) had bilateral choroidal osteomas. The sister was seen at 11 years of age, and the tumor showed significant growth two years later. The twin brothers' tumors were diagnosed at 9 years of age, and their conditions remained stable over two years except for a new, isolated lesion that occurred in one eye of one brother. The siblings' mother had a yellow mottling situated nasal to the disk in each eye that was similar in appearance to that in one eye of one of the twins. She showed no evidence of calcium on ultrasonography. The appearance of osteomas in three siblings suggests a choristoma as the cause of this tumor.

CHOROIDAL OSTEOMA is a benign choroidal tumor most typically found in the peripapillary region in one eye of healthy young females. Histopathologic characteristics of the choroidal osteoma include bone formation with bony trabeculae, blood-filled cavernous spaces, and typical cells seen in bone formation (osteoblasts, osteocytes, and osteoclasts).[1-3]

I studied bilateral peripapillary choroidal osteomas in three siblings, one of whom had considerable tumor growth into the posterior pole over a three-year period of observation and another who showed a new lesion developing at a two-year follow-up examination. The familial occurrence of this lesion has been described previously.[4]

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Case Reports

Information was gathered on three generations of the family pedigree, and seven members from three generations were examined (Fig. 1). All examined members were in excellent general health, and there was no history of consanguinity.

Case 1 (III-1)

The proband, a 13-year-old girl, had enlargement of a bilateral retinal lesion (Fig. 2, top left and right). Two years previously, she had been examined by an ophthalmologist after mild trauma to the left eye. Although no ocular trauma was noted, a white peripapillary lesion in both eyes was found. A recent examination documented that the lesions had enlarged in both eyes.

When I examined the patient, her visual acuity was R.E.: 20/25 and L.E.: 20/30. Her eyes

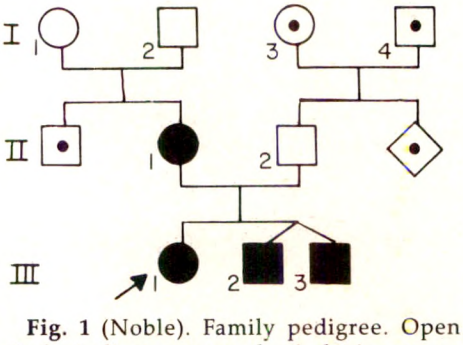

Fig. 1 (Noble). Family pedigree. Open square or circle indicates normal; circle in square or circle, reported normal; solid square or circle, affected.

were normal except for the fundi, which showed bilateral symmetric lesions. They were creamy, yellow-white, deep, irregularly scalloped, and surrounded the optic nerve; they extended nasally, extended temporally along the vascular arcades and beyond, and surrounded the fovea. There was definite significant enlargement of the lesions in all directions when compared with photographs taken two years previously. In areas adjacent to the lesions, there was a coarse pigment mottling.

The patient's visual fields were normal. A contact B-scan ultrasound showed an acoustically reflective echo at the posterior pole of both eyes, which was present at the lowest decibel levels, suggesting the presence of calcium or bone in the posterior aspect of each eye. A diagnosis of choroidal osteoma was made.

Over the next two years, the patient developed bilateral multiple areas of choroidal neovascular membranes at the inferior edge of the fovea associated with metamorphopsia and subretinal hemorrhage and unassociated with any growth of the lesions. These were treated with argon green laser photocoagulation. A hemorrhage under the fovea in the left eye subsequent to laser treatment has resulted in a visual acuity of 20/70, whereas the visual acuity of the right eye has remained at 20/25. Over two years, there has been no growth of the lesions or recurrence of choroidal neovascularization.

Serum values for calcium, phosphorus, alkaline phosphatase, and calcitonin were normal. Results of a chromosomal analysis were normal.

Case 2 (III-2)

The 9-year-old brother of Patient 1 and identical twin of Patient 3 was asymptomatic (Fig. 2, middle left). Routine eye examination disclosed bilateral nasal peripapillary lesions in him and in his twin.

The patient's visual acuity was 20/20 in both eyes. Nasal to the optic nerve in each eye, a deep yellow-white, irregularly scalloped lesion was seen. Additionally, a new lesion was found along the superior temporal vascular arcade in the left eye at the two-year follow-up examination. Areas of mild focal pigment mottling were seen in the posterior pole of each eye. A contact B-scan ultrasound showed a linear echo in the peripapillary region of both eyes, which persisted at the lowest decibel setting.

Case 3 (III-3)

The identical twin of Patient 2 had a visual acuity of 20/20 in each eye (Fig. 2, middle right). A lesion in his left eye was similar to his twin's, whereas the lesion in his right eye appeared as a yellow mottling. Similar areas of focal pigment mottling were seen in the posterior pole of each eye. A contact B-scan ultrasound showed linear densities in the peripapillary region of both eyes, which persisted at the lowest decibel setting. No growth has been observed over two years.

Case 4 (II-1)

The 42-year-old mother of Patients 1, 2, and 3 was asymptomatic with 20/20 visual acuity in each eye. Focal yellow drusen were scattered throughout the fundus. The drusen appeared confluent nasal to the optic nerve in each eye and similar to those in the right eye of Patient 3. There was no evidence of calcium on ultrasonography of either eye.

Case 5 (II-2)

The 43-year-old father of Patients 1, 2, and 3 was asymptomatic and had a visual acuity of 20/20 in each eye. Results of a retinal examination were normal in each eye.

Case 6 (I-1)

The 65-year-old maternal grandmother was asymptomatic with 20/20 visual acuity. She had normal fundi, and results of ultrasonography were normal.

Case 7 (I-2)

The 64-year-old maternal grandfather had a visual acuity of R.E.: 20/50 because of a nuclear sclerosis and L.E.: 20/20. Results of ophthalmoscopic and ultrasonographic examinations were normal in each eye.

Discussion

The salient features of choroidal osteoma have been summarized recently.[5] Most common is a solitary lesion in a peripapillary location in one eye of a young healthy white female. The typical clinical appearance is a sharply circumscribed yellow-white to orange-red lesion with

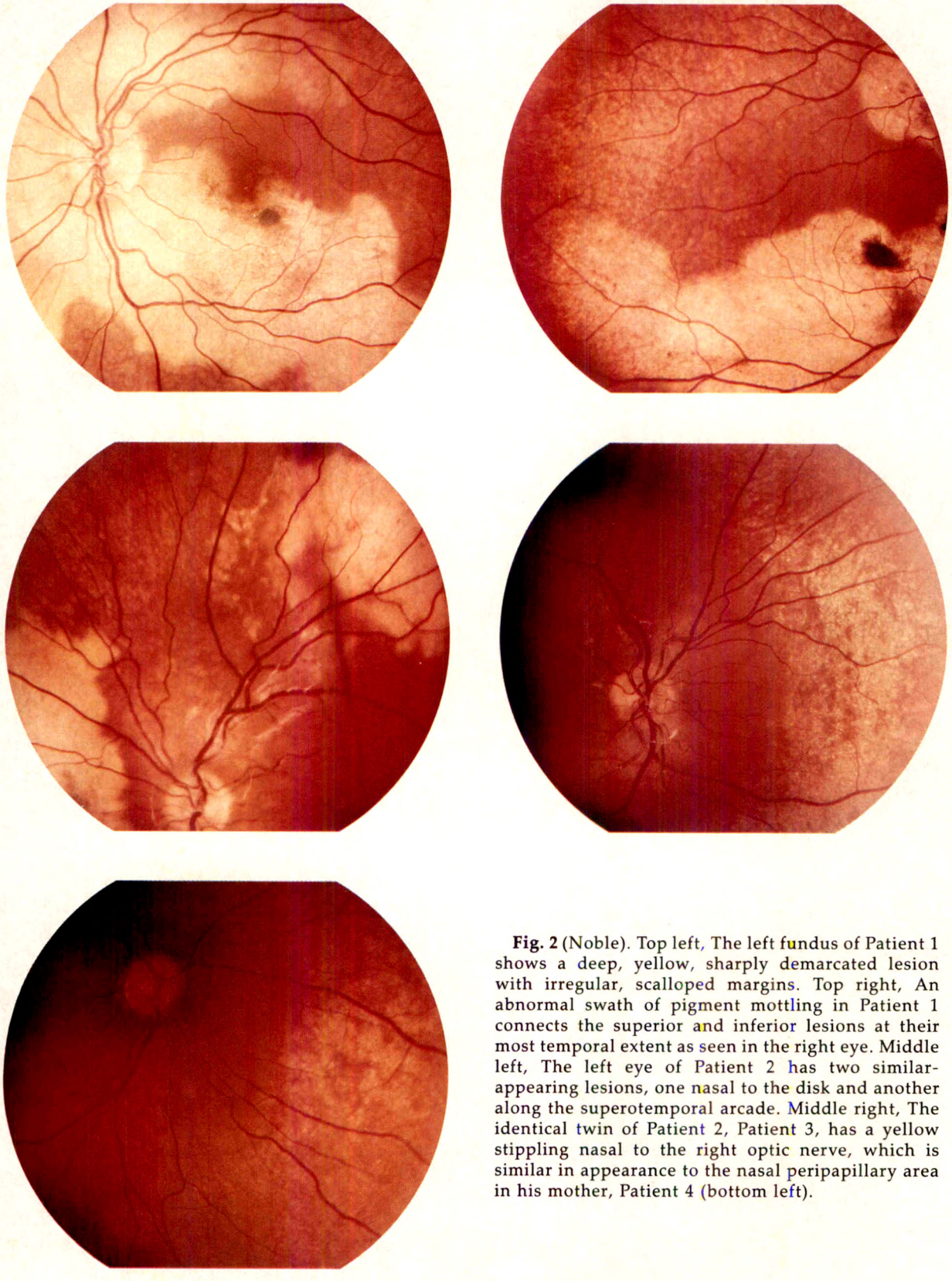

Fig. 2 (Noble). Top left, The left fundus of Patient 1 shows a deep, yellow, sharply demarcated lesion with irregular, scalloped margins. Top right, An abnormal swath of pigment mottling in Patient 1 connects the superior and inferior lesions at their most temporal extent as seen in the right eye. Middle left, The left eye of Patient 2 has two similar-appearing lesions, one nasal to the disk and another along the superotemporal arcade. Middle right, The identical twin of Patient 2, Patient 3, has a yellow stippling nasal to the right optic nerve, which is similar in appearance to the nasal peripapillary area in his mother, Patient 4 (bottom left).

scalloped borders, pseudopod projections, and tufts of branching vessels lying on the surface. Confirmation of bone within the lesions is made by ultrasonographic or radiologic examination.

Two histopathologic studies[1-3] showed normal cancellous bone with dense bony trabeculae and a vascularized fatty marrow containing the normal cellular elements (osteoblasts, osteocytes, and osteoclasts). The bone occupied the choroid and was separated from Bruch's membrane and the retinal pigment epithelium. The cause of the bone formation was not evident.

Growth of these tumors by lateral enlargement has been documented.[6-8] Additionally, a small tumor has been observed to develop de novo in the fellow eye of a patient with an osteoma.[5,6] These tumors have been also been noted to resorb[9,10] and in one instance to decalcify completely.[11]

In one study of choroidal osteoma in a family,[4] the 33-year-old mother had counting fingers visual acuity in each eye since age 11 years and had bilateral peripapillary atrophic chorioretinal lesions. Her 5-year-old daughter had bilateral yellow-white lesions associated with bilateral macular hemorrhages.

The occurrence of the lesions in the family described herein supports the hereditary nature of this disease. The small number of examined family members in both pedigrees makes it difficult to determine the mode of inheritance. This family, however, may represent an autosomal-dominant inheritance with variable expressivity. The mother with the mild peripapillary pigment changes could have had a forme fruste. Alternatively, she could have previously had nasal peripapillary lesions that decalcified.[9-11]

Follow-up studies on the three siblings indicated that growth can occur either by lateral enlargement or by the development of a new lesion at a distant site. Growth occurred in Patients 1 and 2 during puberty, which is a time of accelerated bone growth. Hormonal influences may play a role in the appearance and growth of these tumors.

The pathogenesis of choroidal osteomas is not known, and various causes have been considered. These include a primary congenital tumor of an embryonic tissue rest (choristoma) or secondary ossification and calcification after inflammatory disease, trauma, or other acquired diseases.

A choristoma is a benign tumefaction of a chorista, which is an embryonic tissue rest composed of cellular and tissue elements not normally present at the affected site. Certainly the disease's histopathologic characteristics[1-3] would qualify it as a choristoma. Although osseous choristomas have been described in the epibulbar region,[12] they have not been described in the choroid and retina.

Hamartomas are tumors of an embryonic tissue rest (hamartia) that contain elements usually present at the affected site. Numerous hamartomas have been described in the choroid and retina, and some commonly occur in a peripapillary location. These include astrocytic hamartomas (neurofibromatosis and tuberous sclerosis), retinal capillary hemangiomas (von Hippel's disease), retinal cavernous hemangiomas, retinal arteriovenous anastomotic malformations (Wyburn-Mason syndrome), combined pigment epithelial and retinal hamartomas, and choroidal hemangiomas. With the exception of the last two disorders, these hamartomas are inherited in an autosomal-dominant fashion. Changes in the size and shape of these lesions, including growth, have been documented in some of these hamartomas.

The case for secondary ossification of an acquired disorder is suggested by reports of choroidal osteomas in patients with orbital inflammatory pseudotumor,[9] uveitis and vitreitis,[6,10] possible Harada's disease,[10] and a fatal systemic illness consistent with histiocytosis X.[13] This wide spectrum of disorders lends support to the occurrence of secondary heterotopic bone formation in at least some of these choroidal osteomas. Hormonal influences may play a role because choroidal osteomas occur predominantly in young females, have developed during pregnancy,[14] and have been associated with a transient mild hypoparathyroidism.[9] Additional support for secondary ossification is the appearance of the tumor in previously unaffected adults,[5,6] partial resorption,[9,10] and spontaneous complete decalcification and disappearance.[11]

New lesions and spontaneous resorption of bone, however, are also consistent with a primary choristoma. An embryonic tissue rest of mesenchymal origin may reside in the choroid at birth. This tissue secretes and synthesizes the organic matrix which, in the absence of mineralization, may not be clinically, ultrasonographically, or radiologically evident. In some individuals, mineralization does not occur (perhaps in Patient 4). The mottled pigment

appearance in the posterior pole of the three siblings may be areas of the matrix without mineralization. Subsequent mineralization in an isolated area, such as superiorly in Patient 2, would explain the de novo appearance. If this is true, any area containing the embryonic tissue rest is at risk for mineralization and bone formation.

The stimulus for mineralization is undoubtedly to some degree hormonally controlled. This would explain the early age of onset, the predominance in females, and the previously reported isolated associations with pregnancy[14] and transient hypoparathyroidism.[9] Other possible stimuli for mineralization are inflammations (uveitis,[6,10] Harada's disease,[10] and orbital inflammatory pseudotumor[9]) and systemic illnesses (histiocytosis X).[13]

Under normal conditions, cancellous bone, which is a metabolically active tissue, undergoes continual remodeling, which involves bone formation as well as bone resorption. Because histologic study of a choroidal osteoma shows all the typical cells present in bone formation (osteoblasts, osteocytes, and osteoclasts),[1-3] this could explain both bone growth and partial or complete disappearance. In older individuals, partial or complete resorption of small tumors will not suggest the diagnosis of a choroidal osteoma (possibly as in Patient 4).

The features of the osteoma in the family described herein support choristoma as the cause. These include the tumor appearance in three siblings, a possible forme fruste in the mother, the absence of any inflammatory disease or trauma (except the initial trauma that led to the ocular examination), the early onset, and documented growth in two individuals during puberty. All features point to an inherited congenital tumefaction rather than ossification related to an acquired disorder.

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Risk Factors for Postvitrectomy Fibrin Formation

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We prospectively studied 194 patients undergoing vitrectomy between July 1988 and April 1989 to determine the incidence of postvitrectomy intraocular fibrin formation and the association of a variety of preoperative and intraoperative variables with the formation of severe postvitrectomy fibrin. Overall, 62 (32%) patients developed postvitrectomy fibrin; 25 (13%) had mild fibrin formation, 13 (6.5%) had moderate fibrin formation, and 24 (12.4%) had severe fibrin formation. By logistic multivariate analysis, preoperative factors that were independently predictive of severe fibrin formation included severe flare (P = .004), the presence of a previously placed scleral buckle (P = .001), and poor preoperative visual acuity (P = .007). Anterior epiretinal membrane dissection was the only intraoperative factor that was independently associated with an increased fibrin risk (P = .0003). A risk score derived from the multivariate analysis effectively categorized patients according to their likelihood of developing severe postvitrectomy fibrin. Results of this study may be useful in designing prophylactic interventions to decrease postvitrectomy fibrin formation.

FORMATION of intraocular fibrin may jeopardize surgical success in vitrectomy by a variety of different mechanisms. Occlusion of the pupil by a fibrin pupillary membrane may cause pupillary block glaucoma.[1-3] Intravitreal and epiretinal fibrin may contract, causing traction retinal detachment.[4] It has been hypothesized that fibrin may serve as a surface for cellular proliferation, which could lead to recurrent retinal detachment secondary to proliferative vitreoretinopathy.[5,6] Dense fibrin pupillary membrane or fibrin on the surface of an intraocular lens may preclude adequate postoperative retinal examination.[7]

The incidence and risk factors for the development of postvitrectomy fibrin are not well understood. It is important to identify patients at risk for the development of postvitrectomy fibrin so that prophylactic treatment strategies may be devised. We undertook a prospective study to determine the incidence of this potentially serious complication and to define the preoperative and intraoperative characteristics associated with an increased risk of severe postvitrectomy fibrin formation.

Material and Methods

We prospectively studied all 194 patients who underwent vitrectomy at the Medical College of Wisconsin between July 1988 and April 1989. Each patient underwent a preoperative examination that included a detailed medical and ophthalmologic history. Ocular examination included a measurement of the best-corrected visual acuity, intraocular pressure by applanation tonometry, slit-lamp examination, gonioscopy, and direct and indirect ophthalmoscopy.

Patients were examined postoperatively at 24 and 48 hours by slit-lamp examination and indirect ophthalmoscopy to evaluate the presence of intraocular fibrin. If moderate or severe fibrin was present at 48 hours, patients were subsequently examined at 72 hours. Anterior segment fibrin was graded by slit-lamp examination as previously described.[7,8] Fibrin was designated mild when it was present at the pupillary margin but did not span the pupil. In these instances, fibrin was often present as wispy strands that were adherent to the pupil focally but did not completely bridge the pupillary space. Fibrin was considered moderate when it spanned but did not occlude the pupil.

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Fibrin was graded severe when it completely occluded the pupil. Preoperative anterior chamber cells and flare were graded on an absent to severe (0 to 4+) scale as described previously.[9] All patients received a subconjunctival injection of dexamethasone sodium phosphate at the conclusion of surgery and topical prednisolone acetate postoperatively.

All data were recorded in a uniform manner on a standardized reporting sheet. Factors studied for an association with an increased risk of postvitrectomy fibrin included the following: age, sex, and race; preoperative diagnoses, including diabetic retinopathy, diabetic vitreous hemorrhage, vitreous hemorrhage (nondiabetic), active fibrovascular proliferation secondary to diabetes, active fibrovascular proliferation (nondiabetic), macular pucker, proliferative vitreoretinopathy (grade), rhegmatogenous retinal detachment (type), giant retinal tear, or other, and histories of diabetes (duration), hypertension, or hematologic disorders; preoperative medications; histories of ocular surgery, vitrectomy, scleral buckle, fibrin formation, glaucoma (type), and ocular trauma; preoperative and postoperative visual acuity; results of slit-lamp examination, including flare (grade), cells (grade), rubeosis, and lens (phakic, aphakic, pseudophakic); intraocular pressure; and results of laboratory examination, including blood urea nitrogen levels, creatinine levels, and proteinuria. Intraoperative data collected included duration of surgery (minutes) and the use of any of the following: endolaser (number of spots), drainage retinotomy, retinectomy, scleral buckle (size), gas fill (type), silicone, diathermy, cryopexy, lensectomy, anterior or posterior epiretinal membrane dissection, and iris sutures.

The chi-square test for contingency tables unadjusted for continuity was used to test the association between each variable and severe fibrin formation. To test the association of severe fibrin formation with a given variable after adjusting for other variables, we used multivariate logistic analysis. To identify potentially important preoperative fibrin risk factors, the multivariate analysis was initially conducted on the preoperative variables only. The preoperative variables were then combined with the intraoperative variables, and all the data were subjected to a second multivariate logistic analysis. The strength of association between severe fibrin and a patient characteristic was measured by using the relative odds ratio, which measures the odds of developing severe fibrin formation for patients who have a characteristic divided by the odds of developing severe fibrin formation for patients who do not have the characteristic. The relative odds for a variable after adjusting for other variables can be estimated by taking e (the exponential function of the natural logarithm) to the power of the logistic regression coefficient.[10]

Factors found to be significantly associated with severe fibrin formation on multivariate analysis were used to devise a fibrin risk score. This risk score was used to place patients into three groups (low, medium, and high) on the basis of the predicted risk for severe fibrin formation.

Results

A total of 194 patients were studied. The mean patient age (± S.D.) was 48 ± 22 years. Of the 194 patients, 122 (61%) were men. The preoperative diagnoses are shown in Table 1.

Overall, 62 patients (32%) had postvitrectomy fibrin; 25 (13%) had mild fibrin formation, 13 (6.5%) had moderate fibrin formation, and 24 (12.4%) had severe fibrin formation. There was a statistically significant increased risk of fibrin among patients with proliferative vitreoretinopathy compared to patients without this diagnosis (P = .00). Of 46 patients with proliferative vitreoretinopathy, 31 (67%) developed postvitrectomy fibrin, and of these, 12 (26%) developed severe fibrin. In contrast, 31 of 148 (21%) patients without proliferative vitreoretinopathy developed postvitrectomy fibrin, and of these, 12 (9%) developed severe fibrin. The incidence of postvitrectomy fibrin was not statistically significantly increased among other diagnostic groups.

TABLE 1
PREOPERATIVE DIAGNOSIS IN 194 PATIENTS*

	NO. OF EYES (%)
Macular pucker	43 (22.0)
Trauma	38 (19.4)
Proliferative vitreoretinopathy	46 (23.8)
Rhegmatogenous retinal detachment	60 (30.7)
Vitreous hemorrhage	36 (18.3)
Diabetic traction retinal detachment	43 (22.3)

*Some patients had more than one diagnosis.

TABLE 2
UNIVARIATE ANALYSIS OF PREOPERATIVE VARIABLES ASSOCIATED WITH SEVERE FIBRIN FORMATION

PREOPERATIVE VARIABLES	NO. OF PATIENTS (%) WITH SEVERE FIBRIN FORMATION (N = 24)	NO. OF PATIENTS (%) WITHOUT SEVERE FIBRIN FORMATION (N = 170)	CHI^2	P	ODDS RATIO
Previous ocular surgery	19 (79.2)	90 (52.9)	5.88	.015	3.38
Previous vitrectomy	14 (58.3)	41 (25.6)	10.65	.001	4.06
Previous scleral buckle	16 (66.7)	38 (23.5)	18.94	.000	6.53
Rubeosis	4 (19.1)	10 (6.1)	4.46	.035	3.62
Proliferative vitreoretinopathy	13 (54.2)	33 (19.5)	13.89	.000	4.87
Rhegmatogenous detachment	13 (54.2)	45 (27.3)	7.13	.008	3.15
Hand motions or light perception visual acuity	20 (83.3)	82 (48.2)	10.39	.001	5.37
Aphakia	14 (60.9)	60 (36.1)	5.18	.023	2.75
50 Cells/field	15 (79.0)	60 (40.5)	10.04	.002	5.50
Severe flare	5 (20.8)	3 (1.8)	19.34	.000	14.65

The results of a univariate analysis of variables associated with an increased risk of fibrin formation are shown in Tables 2 and 3. The variables are divided into preoperative patient characteristics and the intraoperative procedures used. Of the preoperative variables, the presence of severe preoperative anterior chamber flare placed the patient at the greatest risk for severe postvitrectomy fibrin (Table 2). Patients with marked flare were 14.56 times more likely to develop severe fibrin than those without this characteristic (P = .000). The second most important preoperative characteristic was the presence of a pre-existing scleral buckle. The third most important factor was the presence of more than 50 cells per high-power field in the anterior chamber as determined by slit-lamp examination. The other preoperative variables listed in Table 2 were also significantly associated with the development of severe fibrin.

The placement of iris sutures to achieve mechanical mydriasis and anterior epiretinal membrane dissection were the intraoperative variables most associated with an increased risk of severe postoperative fibrin on univariate analysis (Table 3). By Student's *t*-test analysis, the operating time was significantly longer among patients who developed severe fibrin postoperatively than among those who did not (P = .000).

The preoperative factors that by multivariate logistic analysis independently predicted severe postoperative fibrin formation are shown in Table 4. Patients with severe anterior chamber flare had a high independent risk of developing severe fibrin. The other factors independently associated with an increased risk were previous scleral buckle and poor preoperative vision. Factors that independently predicted severe postoperative fibrin, when preoperative variables were combined with operative varia-

TABLE 3
UNIVARIATE ANALYSIS OF INTRAOPERATIVE VARIABLES ASSOCIATED WITH SEVERE FIBRIN FORMATION

INTRAOPERATIVE VARIABLES	NO. OF PATIENTS (%) WITH SEVERE FIBRIN FORMATION (N = 24)	NO. OF PATIENTS (%) WITHOUT SEVERE FIBRIN FORMATION (N = 170)	CHI^2	P	ODDS RATIO
C_3F_8 gas	11 (45.8)	26 (15.4)	12.57	.000	4.65
Diathermy	18 (75.0)	77 (45.3)	7.43	.006	3.62
Anterior dissection	18 (75.0)	40 (23.5)	26.58	.000	9.75
Posterior membrane dissection	19 (86.4)	87 (58.4)	6.37	.012	4.51
Iris sutures	6 (27.3)	4 (2.4)	24.17	.000	15.38

TABLE 4
MULTIVARIATE ANALYSIS OF PREOPERATIVE PATIENT CHARACTERISTICS ASSOCIATED WITH SEVERE FIBRIN FORMATION

VARIABLE	LOGISTIC COEFFICIENT	P	ODDS RATIO
Severe flare	3.15	.0004	23.48
Previous scleral buckle	2.22	.0001	9.25
Preoperative visual acuity of hand motions or light perception	1.70	.007	5.49

TABLE 5
MULTIVARIATE ANALYSIS OF PREOPERATIVE AND INTRAOPERATIVE VARIABLES ASSOCIATED WITH SEVERE FIBRIN FORMATION

VARIABLE	LOGISTIC COEFFICIENT	P	ODDS RATIO
Severe flare	4.69	.0001	109.25
Anterior membrane dissection	2.85	.0003	17.32
Previous scleral buckle	1.48	.012	4.41

bles, are shown in Table 5. When the intraoperative variables were combined with the preoperative variables, patients with severe flare still had the highest independent risk of developing severe fibrin (Table 5). For this analysis, the presence of a pre-existing scleral buckle was similarly associated with an increased risk of severe fibrin formation, although anterior epiretinal membrane dissection replaced greater than 50 cells per high-power field as an independent risk factor. Prolonged surgical duration did not independently increase the risk for severe fibrin formation.

Based on the results of the multivariate analysis, we devised a scoring system that was used to place patients into three risk groups (low, medium, and high) according to their likelihood of developing severe postoperative fibrin. The number of patients in each of the risk groups and the corresponding percentage of patients with severe fibrin formation are shown in the Figure. If only preoperative variables were considered, the presence of severe flare alone was sufficient to place patients in the high-risk group. If patients had both a pre-existing scleral buckle and poor preoperative vision, they were also placed in the high-risk group. If they had only one of these latter two variables, they were at moderate risk. The patients were at low risk if none of the three variables were present. If preoperative and operative variables were combined, the presence of severe flare alone also placed patients in the high-risk group. If the patients had both a pre-existing scleral buckle and anterior membrane dissection, they were also at high risk. If only one of these variables was present, they were at moderate risk. If none of the characteristics were present, they were at low risk.

Discussion

Postvitrectomy fibrin formation occurred in 62 (32%) patients. This incidence is similar to that described by Johnson and Blankenship[8] in a small group of patients who underwent vitrectomy surgery. This incidence is higher than that reported in a previous preliminary study.[11] Postvitrectomy fibrin formation was evaluated by slit-lamp examination in this study and by bedside examination with an indirect ophthalmoscope and 20-diopter lens in the previous study.[11] It is possible that the increased incidence of fibrin formation is the result of increased fibrin detection by slit-lamp examination. The incidence of severe fibrin formation

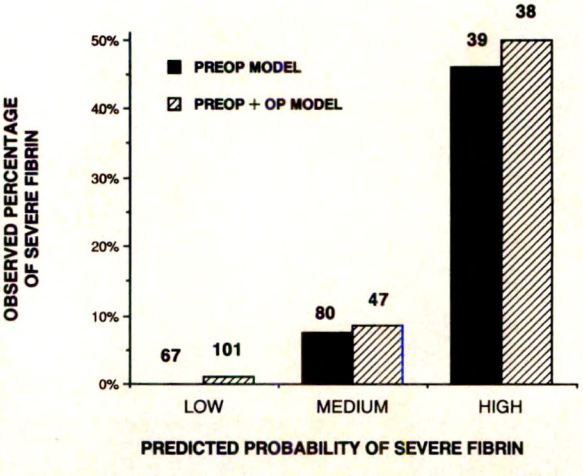

Figure (Jaffe and associates). Rates of severe fibrin formation for subjects in three risk groups as determined by logistic analysis. The numbers above the bars correspond to the number of patients in each risk group.

among all patients undergoing vitrectomy (12%) is likewise similar to the results reported by Johnson and Blankenship.[8] All patients in our study received subconjunctival corticosteroid injections at the conclusion of the surgical procedure, and topical corticosteroids postoperatively. If administering corticosteroids in this manner helped to prevent fibrin formation, it is possible that the incidence of postvitrectomy fibrin among untreated patients would be even higher.

There was an increased incidence of fibrin formation among patients with a preoperative diagnosis of proliferative vitreoretinopathy compared to other preoperative diagnostic groups. Such increased incidence has been suggested previously.[12] It is likely that the increased incidence of severe fibrin formation among patients with proliferative vitreoretinopathy can be attributed in part to the association between proliferative vitreoretinopathy and other preoperative and intraoperative variables. For example, patients with proliferative vitreoretinopathy and rhegmatogenous retinal detachment often have poor preoperative vision, a pre-existing scleral buckle, and ocular inflammation evidenced by anterior chamber cells and flare. Further, they often undergo extensive anterior and posterior epiretinal membrane stripping, injection of C_3F_8 gas, and placement of iris sutures for mechanical mydriasis and diathermy. Each of these preoperative and intraoperative variables were found to increase the risk of severe postvitrectomy fibrin formation on univariate analysis.

Although it has been hypothesized that patients undergoing vitrectomy for complications of diabetes are predisposed to postvitrectomy fibrin,[12-14] we did not find an increased risk of fibrin among diabetic patients, regardless of the fibrin grade. Similarly, Johnson and Blankenship[8] found an increased incidence of postvitrectomy fibrin among patients with proliferative vitreoretinopathy but not among those with diabetes, although the small patient sample size in that study prevented firm conclusions about fibrin incidence. Possibly, the final surgical outcome among diabetic patients with severe postvitrectomy fibrin is worse than that among those without postvitrectomy fibrin. In our study, because the number of diabetic patients with severe fibrin formation was so small, it was not possible to study this statistically. Similarly, although blood urea nitrogen and creatinine levels did not correlate with postvitrectomy fibrin, the small number of patients with abnormal renal function in this study may have masked an actual effect of this variable.

In a preliminary study, we identified risk factors predictive of postvitrectomy fibrin formation.[11] This study is a more comprehensive assessment of preoperative and intraoperative variables predictive of postvitrectomy fibrin. Additionally, patients were stratified on the basis of fibrin severity in this study to better identify factors associated with an increased risk of severe fibrin formation. This outcome is particularly important because eyes that develop severe fibrin are most likely to develop fibrin-related complications, such as pupillary block, traction retinal detachment, and ocular media opacity.[1,4,7] In our study, it was not possible to determine the relationship between fibrin-related complications and severe fibrin because most patients in this group were treated with tissue plasminogen activator. To determine the relationship between severe postoperative fibrin and surgical outcome, it would be necessary to prospectively examine a large group of untreated patients with postoperative fibrin and compare these patients to a group without postoperative fibrin.

In some patients, pupillary dilation by means of topical mydriatics and cycloplegics was inadequate. In these patients, intraoperative iris sutures were placed by using a modification of a previously described technique.[15] The placement of these iris sutures contributed to an increased likelihood of fibrin formation. It is likely that placement of the sutures resulted in irritation and inflammation of the iris, causing a breakdown of the blood-aqueous barrier associated with fibrin deposition. Other techniques for mechanically dilating the pupil intraoperatively have been described.[16] It is not known whether these other techniques would have resulted in a similar increased risk of fibrin deposition postoperatively.

We identified several factors by multivariate analysis that were independently associated with severe fibrin formation. Preoperative factors that were independently predictive of severe fibrin formation after vitrectomy included severe anterior chamber flare, suggesting evidence of breakdown of the blood-aqueous barrier, poor preoperative visual acuity, and a pre-existing scleral buckle. Although the presence of poor visual acuity and a pre-existing scleral buckle indicated a predisposition to severe postvitrectomy fibrin, the reason for this association is unclear.

When the intraoperative variables were com-

bined with preoperative variables in the multivariate analysis, the presence of poor preoperative vision was found to be not as great a risk factor as anterior epiretinal membrane dissection. It is likely that extensive anterior epiretinal membrane dissection increased the mechanical trauma to anterior retinal blood vessels, causing breakdown of the blood-ocular barrier and an increased tendency for severe fibrin formation.

Several variables were associated with severe postvitrectomy fibrin formation on univariate analysis, but were not independently predictive of severe fibrin on multivariate analysis. This phenomenon is most likely the result of the relatedness of various factors. For example, a previous vitrectomy was strongly associated with severe postoperative fibrin formation on univariate analysis. Patients undergoing repeat vitrectomy were also more likely to have a pre-existing scleral buckle and anterior epiretinal membrane dissection. Thus the association of previous vitrectomy and severe fibrin formation could be the result of the interrelation between the pre-existing scleral buckle and anterior epiretinal membrane dissection and previous vitrectomy, and not the previous vitrectomy in itself. Although prolonged operating time was highly associated with severe fibrin formation in the univariate analysis ($P = .00$), when adjustments were made for other intraoperative and preoperative characteristics, operating time did not independently predict severe fibrin formation. It is likely that the effect of increased operating time in the univariate analysis could be accounted for by specific predictive risk factors, such as anterior epiretinal membrane dissection and iris suture placement, that tended to prolong operating time.

The results of this study can be used to design studies of methods to prevent fibrin formation. As indicated in the Figure, the logistic multivariate analysis was effective in separating patients into risk groups on the basis of characteristics predictive of severe fibrin formation. Prophylactic measures have been suggested to prevent postvitrectomy fibrin formation.[8,17]

By selecting patients in the high-risk group for severe fibrin formation, the chances of finding differences in therapeutic effects of alternate prophylactic modalities would be increased.[18] For example, patients at increased risk of postvitrectomy fibrin formation, such as those with severe anterior chamber flare, preexisting scleral buckle, or poor preoperative vision, could be selected for inclusion in a study of this type. Those patients likely to require anterior epiretinal membrane dissection could also be selected for inclusion. In contrast, patients with low risk of severe postvitrectomy fibrin, such as those with a macular epiretinal membrane or diabetic vitreous hemorrhage, could be excluded.

Although all patients received subconjunctival corticosteroids at the conclusion of surgery and topical corticosteroids postoperatively, only an occasional patient was treated with corticosteroids preoperatively. Results from the univariate analysis suggest that prophylactic measures may be useful in the prevention of fibrin formation. For example, the association of preoperative cells and flare, markers for inflammation and breakdown of the blood-aqueous barrier, with postoperative fibrin formation provides the rationale for preoperative use of corticosteroid or nonsteroidal anti-inflammatory agents, or both, in patients with these characteristics. These potential prophylactic measures could be studied prospectively.

Although we found preoperative and intraoperative variables that were predictive of severe fibrin formation, it was not possible to establish causal relationships. Further experimental and clinical studies should be directed at determining whether postvitrectomy fibrin deposition may be lessened by decreasing or eliminating potential risk factors.

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OPHTHALMIC MINIATURE

"Look!" cried the crewman. "Look at his eyes."

"What about them?" asked the brother.

"A moment ago they were gray—as gray as steel cables. Now they're blue!"

"The sun's brighter," said the skipper, shrugging. "Or it's playing tricks with your own eyes. No matter, there's no color in the grave."

Robert Ludlum, *The Bourne Identity*
New York, Richard Marek Publishers, 1980, p. 17

Spontaneous Involution of Subfoveal Neovascularization

Peter A. Campochiaro, M.D., Kirk M. Morgan, M.D., Brian P. Conway, M.D., and John Stathos, M.D.

We studied five patients who maintained or spontaneously regained significant central vision despite the presence of a subfoveal neovascular membrane. Sequential photographs and fluorescein angiograms showed a pattern of development common to these patients and not observed in patients who lose all central vision. The pattern involves formation of a pigmented ring around the subfoveal neovascular membrane followed by alteration of the membrane from one that leaks fluorescein to one that stains but does not leak. This pattern is associated with gradual resorption of subretinal fluid and apparent limitation of subretinal hemorrhage and fibrosis. This course suggests the occurrence of spontaneous involution of some subfoveal neovascular membranes and implicates the retinal pigment epithelium in this process.

THE VISUAL PROGNOSIS for eyes with subfoveal neovascular membranes in age-related macular degeneration is poor.[1,2] Although most eyes with subfoveal neovascular membranes caused by ocular histoplasmosis also have a poor visual outcome, a small percentage retain relatively good visual acuity.[3-7] Some patients with ocular histoplasmosis and subfoveal neovascular membranes undergo spontaneous improvement in visual acuity, often after the onset of visual impairment in the fellow eye.[6,8-10] A similar phenomenon has been noted in patients with age-related macular degeneration; return of central vision, however, is much less common.[11]

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Thus, although most eyes with subfoveal neovascular membranes lose all central vision, a few patients have a relatively good long-term visual outcome. Olk, Burgess, and McCormick[6] identified clinical features in patients with ocular histoplasmosis syndrome and subfoveal neovascular membranes that correlate with a good visual outcome, including age less than 40 years, good initial visual acuity, membrane extent less than 200 μm beyond the center of the foveal avascular zone, and involvement of less than 50% of the foveal avascular zone. The predictive value of these clinical features from the initial examination was confirmed by Kleiner and associates.[7] Little information is available, however, about the course of patients who retain significant central vision despite the presence of a subfoveal neovascular membrane. Over the past five years, we have followed up several such patients.

Case Reports

Case 1

A 30-year-old woman had a six-week history of a central scotoma and metamorphopsia in her left eye. Visual acuity was R.E.: 20/20 and L.E.: 20/40. Ophthalmoscopic examination disclosed that the right eye was normal and that the left eye had a subretinal lesion with a fleck of subretinal blood and an overlying serous detachment. There were no peripheral chorioretinal scars or peripapillary atrophy. Fluorescein angiography showed a subretinal neovascular membrane involving the center of the foveal avascular zone (Fig. 1, top). No treatment was offered.

On follow-up examination three months later, visual acuity had dropped to L.E.: 20/100. There was pigment along the border of the subfoveal neovascular membrane and a rim of surrounding subretinal blood. The overlying serous detachment was larger. Three months later, visual acuity was L.E.: 20/80, the pig-

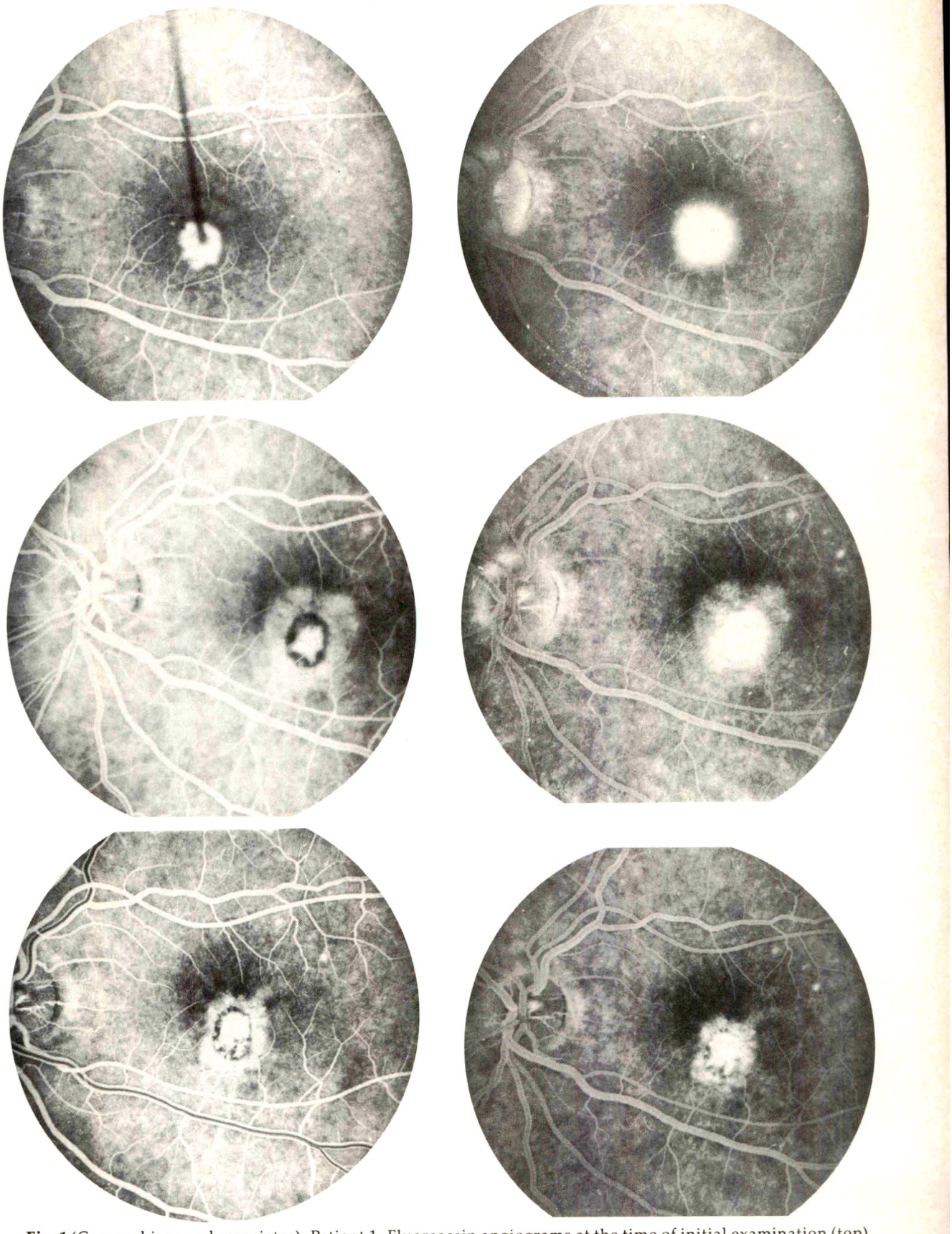

Fig. 1 (Campochiaro and associates). Patient 1. Fluorescein angiograms at the time of initial examination (top), six months later (middle), and 2½ years later (bottom). Note the ring of blocked fluorescence from the pigmented ring.

ment surrounding the subfoveal neovascular membrane was denser, much of the surrounding blood had resorbed, and the serous detachment was smaller. Six months later visual acuity was L.E.: 20/80. The subretinal lesion was slightly smaller with an atrophic area surrounding it. The serous detachment was unchanged, and fluorescein angiography showed persistent leakage from the subfoveal neovascular membrane (Fig. 1, middle). Six months later, visual acuity was R.E.: 20/20 and L.E.: 20/70. The subretinal lesion was replaced by a gray scar in the center of the macula with a shallow overlying serous detachment. Over the next year, the serous detachment resolved and on the last follow-up examination, 2½ years after the initial examination, visual acuity was R.E.: 20/20 and L.E.: 20/25 with a flat scar in the macula that stained with fluorescein but did not leak (Fig. 1, bottom).

Case 2

A 34-year-old woman known to have ocular histoplasmosis syndrome had an acute onset of blurred visual acuity and a subretinal hemorrhage in her left eye. Visual acuity was R.E.: 20/20 and L.E.: 20/40 − 2. Ophthalmoscopic examination showed several punched-out chorioretinal scars in the right eye, and in the left eye there was a subretinal hemorrhage in the fovea, an overlying serous detachment, and several small chorioretinal scars in the periph-

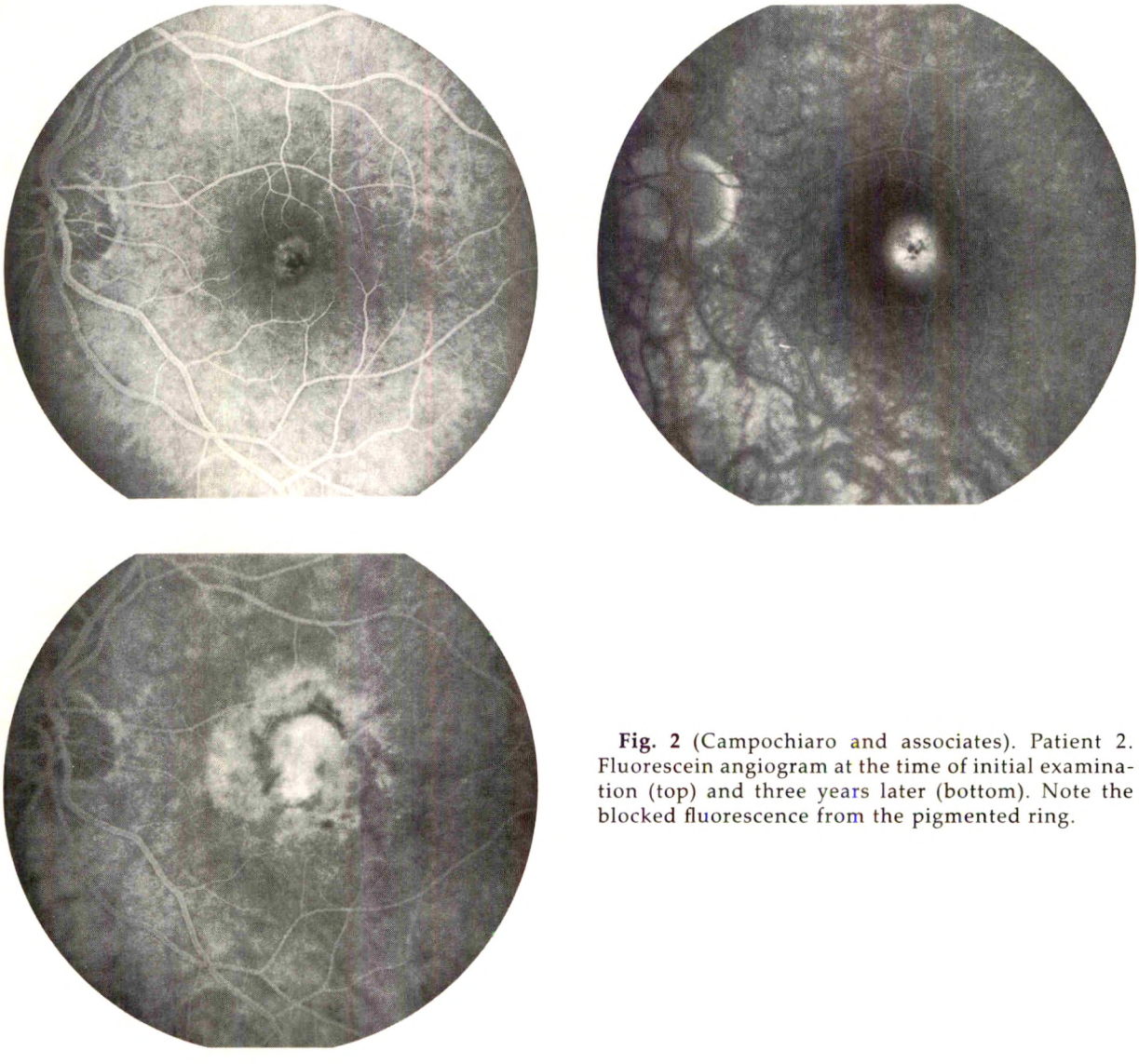

Fig. 2 (Campochiaro and associates). Patient 2. Fluorescein angiogram at the time of initial examination (top) and three years later (bottom). Note the blocked fluorescence from the pigmented ring.

ery. Fluorescein angiography showed a subfoveal neovascular membrane (Fig. 2, top). No treatment was offered.

The patient returned for a follow-up examination five months later, noting that her visual acuity had deteriorated shortly after her first examination and had remained stable since then. Visual acuity was L.E.: 20/200, and ophthalmoscopic examination showed a subfoveal pigment ring with a small hemorrhage at its inferior border and an overlying serous detachment. Over the next 30 months, the pigment became less prominent, the blood resorbed, and visual acuity improved to 20/40. Fluorescein angiography showed staining, but no leakage within the flat macular scar (Fig. 2, bottom left).

Case 3

A 52-year-old man had decreased visual acuity and metamorphopsia in his right eye. He had noted the problem six weeks before the time of referral. Visual acuity was R.E.: 20/50 − 2 and L.E.: 20/20. Ophthalmoscopic examination showed peripapillary atrophy with peripheral chorioretinal scars in both eyes and a subfoveal lesion with a lightly pigmented ring and an overlying serous detachment in the right eye. Fluorescein angiography showed a subfoveal neovascular membrane in the right eye

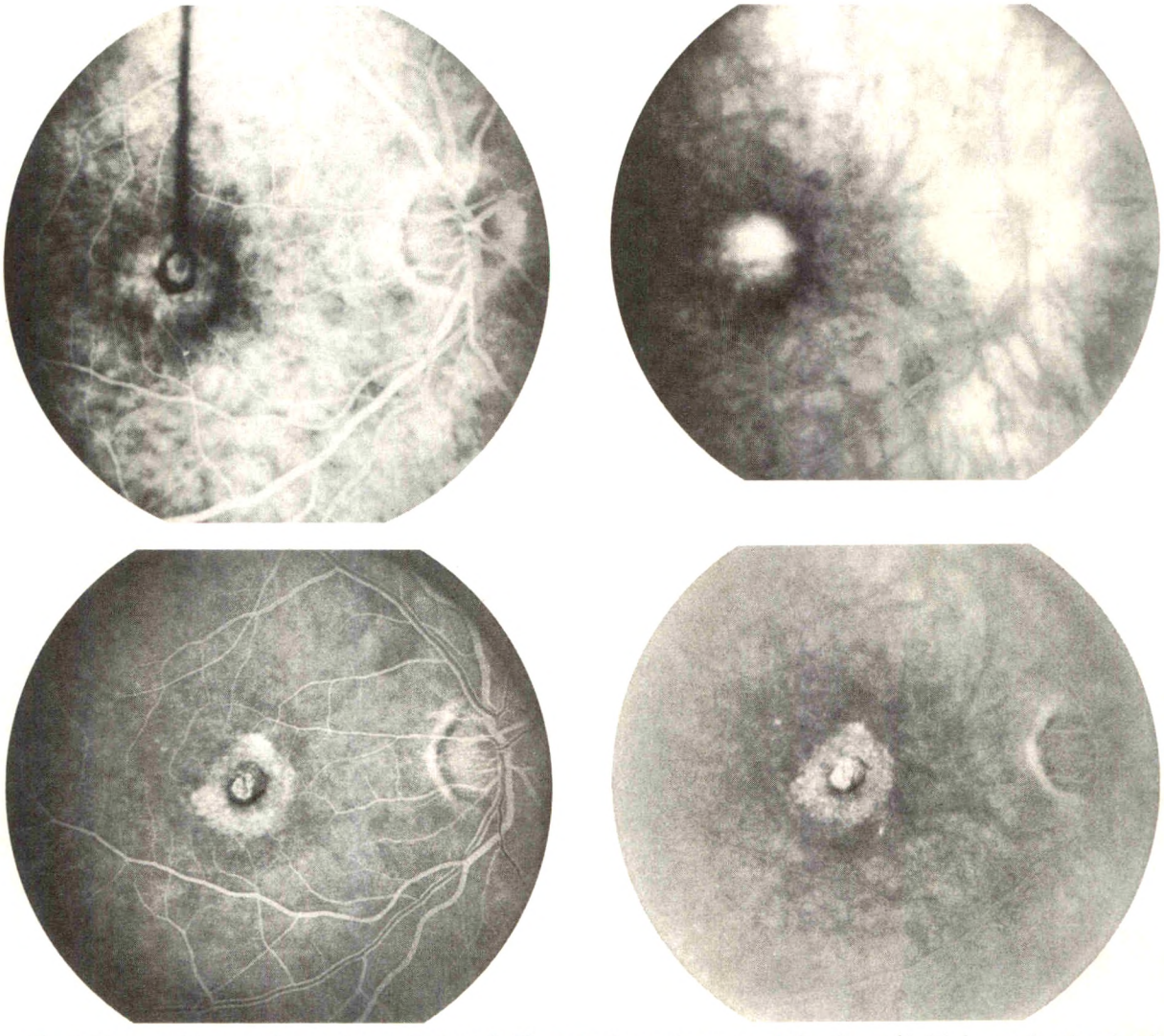

Fig. 3 (Campochiaro and associates). Patient 3. Fluorescein angiograms at the time of initial examination (top) and 4½ years later (bottom). Note the blocked fluorescence from the pigmented ring.

(Fig. 3, top). No treatment was recommended. The patient has been followed up for 4½ years, and visual acuity has remained R.E.: 20/50, with increased pigment surrounding the subfoveal lesion and resolution of the serous detachment. Fluorescein angiography 4½ years after the initial examination showed staining, but no leakage in the flat macular scar (Fig. 3, bottom).

Case 4

A 32-year-old woman complained of decreased visual acuity and metamorphopsia of two weeks' duration in her right eye. Visual acuity was R.E.: 20/70 and L.E.: 20/20. Ophthalmoscopic examination showed a white subfoveal lesion with a few surrounding flecks of blood and overlying serous detachment. Fluorescein angiography showed a subfoveal neovascular membrane (Fig. 4, top left). A brief course of oral corticosteroids was given without improvement.

Two months after examination, visual acuity was R.E.: 20/200 and L.E.: 20/20. The subfoveal lesion was unchanged, but the serous detachment was slightly larger. On follow-up examination five months later, visual acuity was R.E.: 20/100, and a pigmented ring was noted around the macular lesion that was otherwise unchanged. Nine months later (15 months after the initial examination), visual acuity was still R.E.: 20/100, and fluorescein angiography showed persistent leakage from the area of the subfoveal neovascular membrane that was slightly larger than it was at the time of the initial examination (Fig. 4, top right). One year later, visual acuity was R.E.: 20/40 and L.E.:

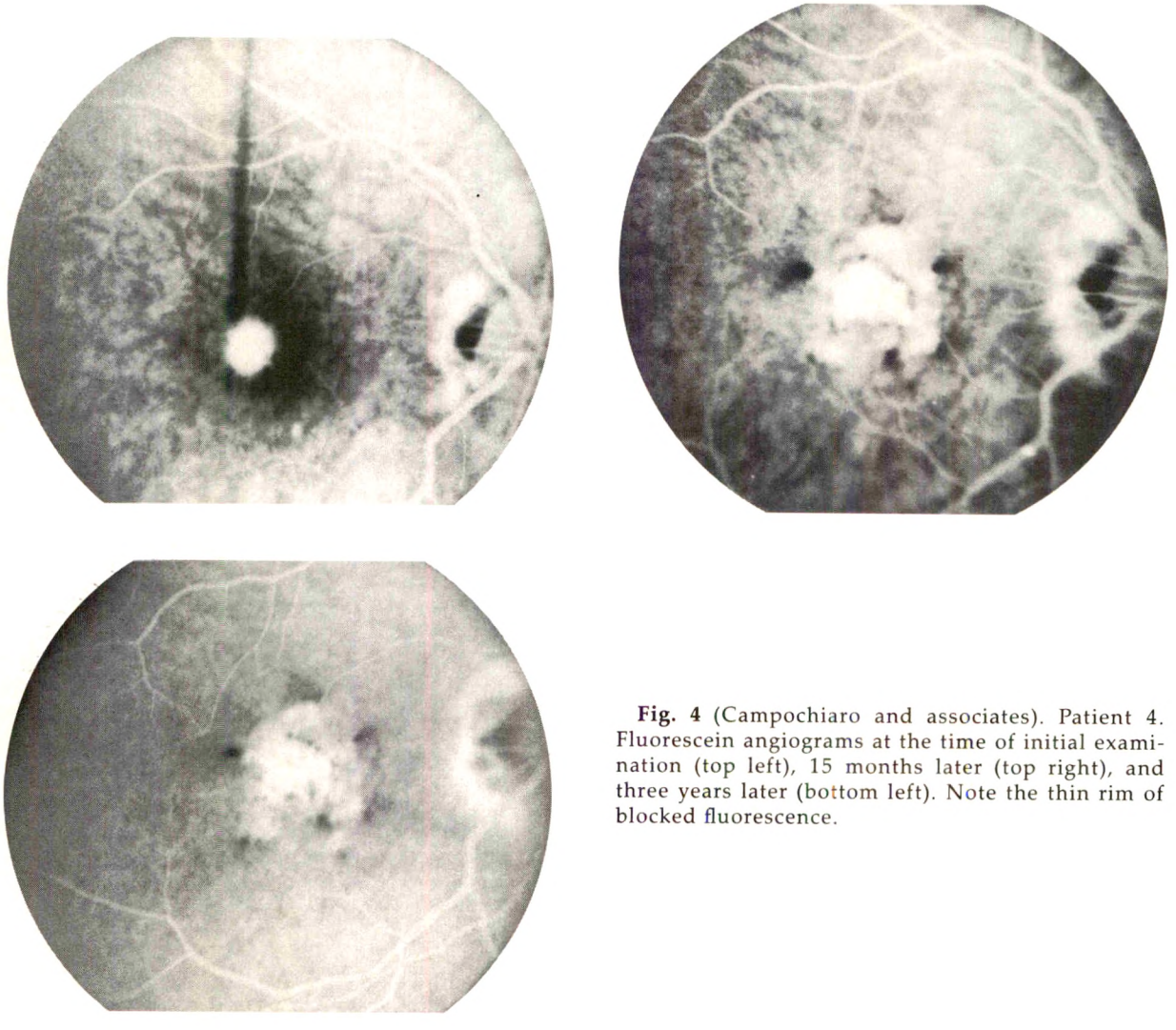

Fig. 4 (Campochiaro and associates). Patient 4. Fluorescein angiograms at the time of initial examination (top left), 15 months later (top right), and three years later (bottom left). Note the thin rim of blocked fluorescence.

20/30. There was a flat scar in the macula of the right eye and several histo spots in the macula of the left eye. The patient returned one year later complaining of a gradual decrease in visual acuity in the left eye. Visual acuity was R.E.: 20/40 and L.E.: 20/200. There was no change in the subfoveal scar in the right eye, but in the left eye there was a serous detachment involving the fovea with a small subretinal hemorrhage along its inferior border. Fluorescein angiography showed a new subfoveal neovascular membrane in the left eye and staining of (but no leakage from) the subfoveal scar in the right eye (Fig. 4, bottom). Over the next 2½ years, there was gradual improvement in the left eye, and on last follow-up examination (5½ years after the onset of the subfoveal neovascular membrane in the right eye) visual acuity was 20/60 in each eye with flat macular scars in both eyes.

Case 5

A 32-year-old woman had decreased vision and metamorphopsia in her right eye. Visual acuity was R.E.: 20/164 and L.E.: 20/20. Ophthalmoscopic examination showed a serous detachment of the macula with subretinal hemorrhage at its borders in the right eye and several punched out chorioretinal scars in the midperiphery of both eyes. Fluorescein angiography confirmed the presence of a subfoveal neovascular membrane in the right eye (Fig. 5, left). No treatment was recommended, and over the next 12 months the serous detachment in the right eye resolved with improvement of visual acuity to 20/30. Three years later, visual acuity was R.E.: 20/25 with a flat macular scar that showed staining but no leakage on fluorescein angiography (Fig. 5, right).

Discussion

The patients' case histories disclose several similarities. The patients tended to be young and have ocular histoplasmosis syndrome, but some patients had other disease processes. They usually had a modest decrease in visual acuity that frequently deteriorated in association with worsening of serous detachment of the macula. Small subretinal hemorrhages and mild subretinal exudation occurred in some patients, but in no patient was a large amount of subretinal hemorrhage or exudate noted. In each patient, a pigmented ring formed around the subfoveal neovascular membrane. The pigmented rings were not always prominent, and the amount of pigmentation varied throughout the course. Over 12 to 36 months, the serous detachments resolved leaving flat, gray macular scars, and several patients had significant improvement in visual acuity associated with fluo-

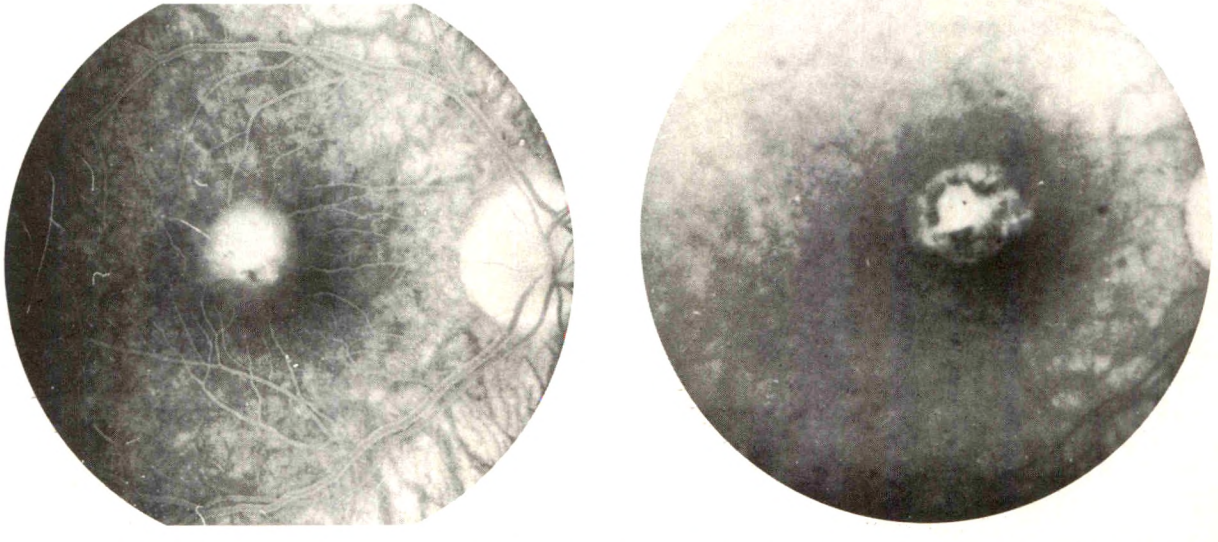

Fig. 5 (Campochiaro and associates). Patient 5. Fluorescein angiograms at the time of initial examination (left) and three years later (right). Note the blocked fluorescence from the pigmented ring.

rescein angiograms that showed staining within the scar, but no significant leakage.

The course in these patients suggests spontaneous involution of subfoveal neovascular membranes, because fluorescein angiograms showed that leaking subfoveal lesions were replaced by nonleaking scars. The mechanism of visual loss and recovery is not known, but the loss and recovery appear to coincide with worsening and improvement in serous detachment of the macula. It is known that visual recovery can occur after resolution of prolonged serous detachment of the macula in the setting of normal-appearing retinal pigment epithelium, but the patients described herein had areas of hypopigmentation and hyperpigmentation suggesting abnormal underlying retinal pigment epithelium. It may be, however, that within the macular scars there was functioning retinal pigment epithelium that permitted functioning of some foveal or parafoveal cones. An alternative explanation is that the scarring was sufficiently limited to allow functioning of parafoveal cones adjacent to the scar. In either case, the critical factor appears to be the limitation or alteration of scarring that occurs in association with subretinal neovascularization.

Limitation or alteration of scarring that results in a good visual outcome in a small number of patients with subfoveal neovascular membranes has important implications for all patients with subretinal neovascularization. Elucidation of the mechanisms involved could provide a basis for therapeutic strategies other than laser photocoagulation. The first step in clarifying the mechanism is to define what distinguishes these patients from most patients with subfoveal neovascular membranes who experience loss of central visual acuity. Our group of patients suggests that one possible difference is the occurrence of a pigmented ring surrounding the subretinal neovascular membrane.

The occurrence of pigmented rings around subfoveal neovascular membranes has also been noted in several previous studies. Gass and Wilkinson[3] described a 32-year-old woman with ocular histoplasmosis syndrome who regained 20/20 visual acuity despite a small disciform scar that extended beneath the fovea. The fundus photographs of this patient show a typical pigmented ring with a surrounding depigmented halo as is seen in our patients. Thirty-three of 81 (37%) patients with ocular histoplasmosis syndrome described by Gass and Wilkinson[3] had pigmented rings, but no prognostic significance was discussed. Gutman[12] described a 32-year-old man who recovered 20/15 visual acuity after resolution of a serosanguineous detachment associated with an extrafoveal lesion that had developed a pigmented ring and a surrounding area of mottled fluorescence on fluorescein angiography. Baskin and associates[13] described a 30-year-old woman who had bilateral parafoveal membranes with surrounding hyperpigmented and hypopigmented rings and good visual acuity. Thus other authors have also noted an association between the formation of a pigmented ring surrounding a subretinal neovascular membrane and a favorable visual outcome.

Another important prognostic factor is age. Two previous studies[6,7] have shown that young age correlates with a good visual outcome in patients with ocular histoplasmosis and subretinal neovascular membranes, and four of our five patients were in their early 30s. Young patients may be more likely to undergo spontaneous involution of subfoveal neovascular membranes and therefore have a better visual prognosis.

The reason for the association of young age, a surrounding pigmented ring, and spontaneous involution of subfoveal neovascular membranes is currently unknown, but there is the possibility that young retinal pigment epithelium may function to impede the growth of subfoveal neovascular membranes and promote their involution, functions that it loses with age. This possibility is supported by experimental observations. Laser-induced subretinal neovascular membranes in young primates become engulfed by retinal pigment epithelial cells.[14,15] Vascular endothelial cells produce chemoattractants for retinal pigment epithelium in vitro,[16] and it is possible that choroidal new vessels release a similar substance that results in their envelopment by retinal pigment epithelium. Such envelopment could alter vascular invasion and associated scarring in several ways. In the primate model, such envelopment was noted to limit fluorescein leakage from subfoveal neovascular membranes,[14,15] and this preservation of the blood-retinal barrier, even if incomplete, might help to limit scarring. Engulfment of subfoveal neovascular membranes by retinal pigment epithelium might also limit their bleeding, and subretinal hemorrhage is a potent stimulus for fibrosis. Additionally, there is in vitro evidence to suggest that under certain circumstances retinal pigment epithelial cells may release substances that could help to bring about involution of

subretinal neovascular membranes.[17,18] Thus, over time, healthy retinal pigment epithelium may be able to repel vascular invasion of the subretinal space and limit its damaging effects.

Some functions of the retinal pigment epithelium may decline with advancing age, and it has been suggested that the retinal pigment epithelium is the site of the primary insult in age-related macular degeneration.[19] Diseased retinal pigment epithelium may not only lack functions that help it to limit subretinal neovascular membranes, but may actually exacerbate the process. It has been shown that under certain conditions in vitro, retinal pigment epithelium can produce stimuli that may favor neovascularization.[20-22] Retinal pigment epithelial cells secrete growth-promoting activity for vascular endothelial cells,[20,21] they can produce basic fibroblast growth factor,[22] and we have recently shown that they can produce a plasminogen activator as well as an inhibitor of plasminogen activator.[18] Thus it may be that the role of the retinal pigment epithelium in the control of subretinal neovascularization depends on the balance between inhibitory and stimulatory activities and that in young patients conditions tend to favor the former, whereas in older patients they invariably favor the latter.

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Patterns of Rod and Cone Dysfunction in Bardet-Biedl Syndrome

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We studied visual function in 16 patients with the Bardet-Biedl syndrome. Visual acuity, kinetic perimetry, and electroretinography results indicated a severe loss of central and peripheral vision and rod and cone function by the second or third decade of life. Light- and dark-adapted static perimetry in patients 10 to 15 years of age with early involvement showed a parallel and marked loss of rod and cone sensitivity across the visual field. Patients with more advanced disease and no measurable peripheral visual field showed different patterns of central visual dysfunction: an island of only cone function centered in a bull's-eye lesion; patches of rod function surrounding geographic atrophy; or a central island of excellent rod sensitivity but severely impaired cones. In the two least-affected patients, a 13-year-old boy and the asymptomatic 45-year-old sibling of a patient, there were more rod than cone abnormalities as determined by electroretinography and static perimetry.

PATIENTS WITH THE BARDET-BIEDL syndrome can have many of the following abnormalities: retinal degeneration, polydactyly, obesity, mental retardation, and genitourinary anomalies. The abnormalities in visual function associated with this retinal degeneration have been studied mainly by electroretinography and with dark-adapted thresholds at single retinal loci.[1-7] There is no consensus in earlier studies about the pattern of rod- and cone-mediated dysfunction in this retinopathy. There are reports of more cone than rod malfunction,[2,6] more rod than cone abnormalities,[3,7] and equal impairment of rod and cone systems.[4]

To characterize the patterns of visual dysfunction in the Bardet-Biedl syndrome, we studied 16 patients who had the syndrome by using not only traditional clinical measures of visual function but also psychophysical techniques that permit assessment of the regional retinal variations of rod- and cone-mediated function. In some of the younger patients with normal intelligence, dark- and light-adapted static thresholds were measured throughout the visual field, thus permitting a comparison with results using similar methods in typical retinitis pigmentosa and cone-rod dystrophy.[8,9] An unusually mild expression of the retinopathy in an asymptomatic sibling of one of the patients was also investigated. We published some of our findings previously.[10]

Patients and Methods

The diagnosis of Bardet-Biedl syndrome was made for 16 patients in this study because they had polydactyly, obesity, and retinal degeneration. Five of the patients were of subnormal intelligence, four patients had known urologic abnormalities, and one patient had adult-onset diabetes mellitus. None of the patients had iris colobomas, deafness, or ataxia.[6,11] Five patients were considered to have autosomal-recessive inheritance because there was a history of parental consanguinity and the parents had reportedly normal vision; two of these five patients were siblings. Nine patients had no known affected relatives (simplex) and another pair of siblings had more than one affected in the sibship (multiplex).[12] Five other patients were studied: the sibling of one of the Bardet-

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Biedl patients, the mothers of two of the patients, and two patients with typical retinitis pigmentosa. All subjects gave informed consent after a full explanation of the procedures was provided.

Kinetic visual fields were performed with a calibrated Goldmann perimeter in 14 patients. Targets V (64 mm^2 area) and I (0.25 mm^2 area) were used at intensity 4e (318 cd/m^2) on the 10-cd/m^2 white background. The test targets were moved from nonseeing to seeing areas. Visual field area with the V_{4e} target was quantified by computer as described previously[13]; results in patients are expressed as a percent of the normal mean area. In eight patients, the kinetic boundaries of the central islands of vision were determined with a modified fundus photoperimeter (45-degree field). With this technique, the visual field is measured while viewing the fundus, and the result is recorded photographically. The fundus photograph with superimposed visual field permits correlation of function with fundus structure. Details of the instrumentation and testing technique have been published.[14]

Full-field rod and cone electroretinograms were performed in all but one of the patients. The electroretinograms were elicited, recorded, and analyzed with methods previously described.[9,13]

Static threshold perimetry was performed in 11 patients in the dark-adapted state by using 500- and 650-nm stimuli (target area, 64 mm^2) and in the light-adapted state with a 600-nm stimulus. The instrumentation and testing techniques have been described.[15,16] Among the threshold test strategies used in this study were a full-field test of 75 loci (12-degree grid); horizontal profile tests (spacing of 2 degrees in the central 60 degrees and 12 degrees at greater eccentricities); and a macula test with 17 loci on a 2-degree grid covering a square central field, 6 degrees on a side. The sensitivity difference between the 500- and 650-nm stimuli was used to determine whether rods, cones, or both rods and cones mediated detection of the targets at each test locus in the dark-adapted state. For each locus, sensitivity losses were calculated for rods (based on 500-nm test results, dark-adapted) and for cones (based on either 650-nm test results, dark-adapted, or 600-nm test results, light-adapted) by comparison to normal mean values. Analysis methods and normal results have been published.[9,14,17] Two-color dark adaptometry was performed with 500- and 650-nm stimuli.[9,14,15]

Results

Ocular findings in the Bardet-Biedl patients are shown in the Table. Most of the patients were myopic with some astigmatism. Nystagmus was present in six patients (Patients 8 and 11 to 15). The lenses in five of the older patients (Patients 11 to 14 and 16) had small central posterior subcapsular cataracts, and cells were seen in the vitreous of all patients. On fundus examination, all patients had attenuated retinal vessels and waxy pallor of the optic disk. In the peripheral fundus of some patients, there were retinal pigment epithelial changes including bone spicule-like pigment. In the macula, there were abnormalities such as minimal pigmentary disturbances, a wrinkled appearance, depigmentation in a ring around an intact central area (bull's eye), and geographic atrophy of the retinal pigment epithelium.

Clinical measures of visual function—Clinical tests of visual function (Snellen visual acuity, color vision, full-field electroretinograms, and Goldmann kinetic perimetry) were performed in most patients. All patients had abnormal visual acuity (Table). No patient had a visual acuity of better than 20/40 even at the earliest ages tested, and the most abnormal visual acuities were in five of the six patients over 24 years of age. Results of color vision testing with the Farnsworth panel D-15 were abnormal without a specific axis in the ten patients who were able to perform the test.

There were no detectable rod electroretinograms (despite computer averaging) over a range of stimulus intensities[9,18] in the 15 patients tested. Eight patients had recordable cone signals that were markedly reduced in amplitude (range of amplitudes for cone flicker electroretinogram, 5 to 10 μV; normal mean, 98 μV; S.D., 24 μV; N = 37[9]) and delayed in implicit time (range of timing, 43 to 50 msec; normal mean, 26.9 msec; S.D., 1.0 msec; N = 37[9]). The cone flicker electroretinogram in Patient 6 was considerably greater in amplitude than those of the other patients (50 μV) but markedly delayed in timing (45 msec). Patients 5, 7, 11, 12, 14, and 15 had nondetectable rod and cone electroretinograms.

Goldmann kinetic visual fields for the left eyes of three patients are shown in Figure 1. Patient 1, age 10.3 years, had a relatively full field to the V_{4e} test target, but the field with the I_{4e} was limited to a small central island. Patient

TABLE
OCULAR FINDINGS IN 16 PATIENTS WITH BARDET-BIEDL SYNDROME

PATIENT NO., FAMILY NO., AGE AT FIRST VISIT* (YRS), SEX	GENETIC TYPE		VISUAL ACUITY AT FIRST VISIT†	REFRACTION	FUNDUS ABNORMALITIES (SIMILAR IN BOTH EYES)‡ MACULA	PERIPHERY
1, 1, 10.3, F	Autosomal recessive	R.E.	20/70	−1.00 − 4.50 × 175	—	—
		L.E.	20/70	+0.25 − 4.25 × 175		
2, 2, 10.4, F	Autosomal recessive	R.E.	20/100	−2.25 − 3.50 × 30	—	Tigroid, bone spicule-like pigment
		L.E.	20/80	−4.25 − 3.25 × 165		
3, 3, 11.1, F	Autosomal recessive	R.E.	20/100	+1.75 − 1.25 × 180	Wrinkling, —	—
		L.E.	20/100	+1.75 − 1.25 × 180		
4, 4, 11.9, M	Simplex	R.E.	20/80	+1.00 − 1.25 × 165	Depigmentation	—
		L.E.	20/80	−1.25 − 0.75 × 175		
5, 5, 11.9,* M	Autosomal recessive	R.E.	20/70	−0.50 − 1.75 × 180	Bull's eye lesion	Bone spicule-like pigment
		L.E.	20/70	Plano − 1.75 × 180		
6, 6, 13.2, M	Simplex	R.E.	20/400	+1.50 − 1.50 × 15	Depigmentation, wrinkling	Pigment mottling
		L.E.	20/80	+1.00 − 1.75 × 5		
7, 2, 14.8, F	Autosomal recessive	R.E.	20/200	+0.50 − 4.50 × 15	—	Bone spicule-like pigment
		L.E.	20/200	−0.25 − 4.25 × 180		
8, 7, 15.5,* F	Simplex	R.E.	20/100	+3.50 − 2.00 × 170	Bull's eye lesion	Bone spicule-like pigment
		L.E.	20/100	+3.25 − 1.75 × 2		
9, 8, 17.3,* M	Multiplex	R.E.	20/40	Plano − 1.00 × 155	Bull's eye lesion, wrinkling	Tigroid, bone spicule-like pigment
		L.E.	20/50	−0.25 − 0.75 × 5		
10, 8, 19.2,* F	Multiplex	R.E.	20/40	Plano − 1.25 × 175	Bull's eye lesion, wrinkling	Tigroid, bone spicule-like pigment
		L.E.	20/40	Plano − 1.00 × 5		
11, 9, 24.8, M	Simplex	R.E.	H.M.	−4.25 − 1.75 × 180	Bull's eye lesion	Bone spicule-like pigment
		L.E.	H.M.	−3.25 − 1.75 × 180		
12, 10, 25.2,* F	Simplex	R.E.	2/200	−14.75 − 4.00 × 14	Depigmentation	Tigroid, bone spicule-like pigment
		L.E.	20/200	−14.25 − 4.25 × 163		
13, 11, 27.2, M	Simplex	R.E.	20/200	−3.00 − 3.50 × 22	Depigmentation, wrinkling	Bone spicule-like pigment
		L.E.	4/200	−2.25 − 4.00 × 172		
14, 12, 31.4, M	Simplex	R.E.	20/60	−1.00 − 1.00 × 85	Wrinkling, —	Tigroid, bone spicule-like pigment
		L.E.	20/70	−1.00 − 0.75 × 82		
15, 13, 37, F	Simplex	R.E.	2/200	−0.50 − 2.00 × 10	Depigmentation	Bone spicule-like pigment
		L.E.	1/200	+0.25 − 2.00 × 173		
16, 14, 43.8, M	Simplex	R.E.	20/400	−2.25 − 0.75 × 15	Geographic atrophy	Tigroid, bone spicule-like pigment
		L.E.	5/200	−1.50 − 1.75 × 5		

*Multiple visits.
†H.M. indicates hand motions.
‡—indicates no obvious pigmentary disturbances.

8, at age 21.6 years, retained some nasal and temporal peripheral islands of vision separated from a small central island by an annular scotoma; the I_{4e} target was not detected. Patient 12, at age 25.1 years, had only a small central island of vision with the V_{4e}, and there was no detection of the I_{4e} target.

The relationship of kinetic visual field area (with the V_{4e} target) to age for the study population is also shown in Figure 1. The graph indicates that the patients under 15 years of age had considerable expanse of visual field. Except for Patient 13 who retained small islands of function in the peripheral field, the patients over 24 years of age had only a central island of vision; two patients showed this severe degree of peripheral field loss by ages 17 and 19 years. Patient 8 was tested on two visits separated by

almost four years. On the earlier visit, at age 17.7 years, the field to V_{4e} was relatively full except for scotomas in the midperipheral field; at age 21.6 years, the field had decreased in extent by almost 40%. None of the patients showed more than a small central island when tested with the I_{4e} target.

Rod and cone perimetry—The distribution and degree of rod- and cone-mediated dysfunction in the visual field were measured in four young patients with normal intelligence: Patients 1, 2, 6, and 7. The results of two-color dark-adapted static perimetry along the horizontal meridian in normal subjects (N = 10; ages, 13 to 59 years) and in Patients 1 and 7 are shown in Figure 2. Sensitivity levels to the 500- and 650-nm stimuli are displayed in the upper graphs, and the sensitivity differences between the two colors are shown in the lower graphs. For the normal subjects, mean extrafoveal sensitivity to 500 nm varied between 60 and 70 dB, and to 650 nm it varied between 30 and 40 dB across the visual field. Sensitivity differences indicate that except at and near the foveal locus, there is rod photoreceptor mediation; more centrally, there can be mixed rod and cone mediation of detection.[15,17] In Patient 1, a 10-year-old girl, rod sensitivity was reduced by about 4 log units at the two loci with measurable function in the far temporal peripheral field. There was no measurable sensitivity to either color from about 30 to 60 degrees. At 20 to 30 degrees from fixation, there was rod-mediated sensitivity, which was reduced by about 3 to 3.5 log units to 500 nm. Loci in the central 8 degrees were either mixed or cone-mediated. At the mixed loci, sensitivity to 500 nm (representing rod function) was also about 3 to 3.5 log

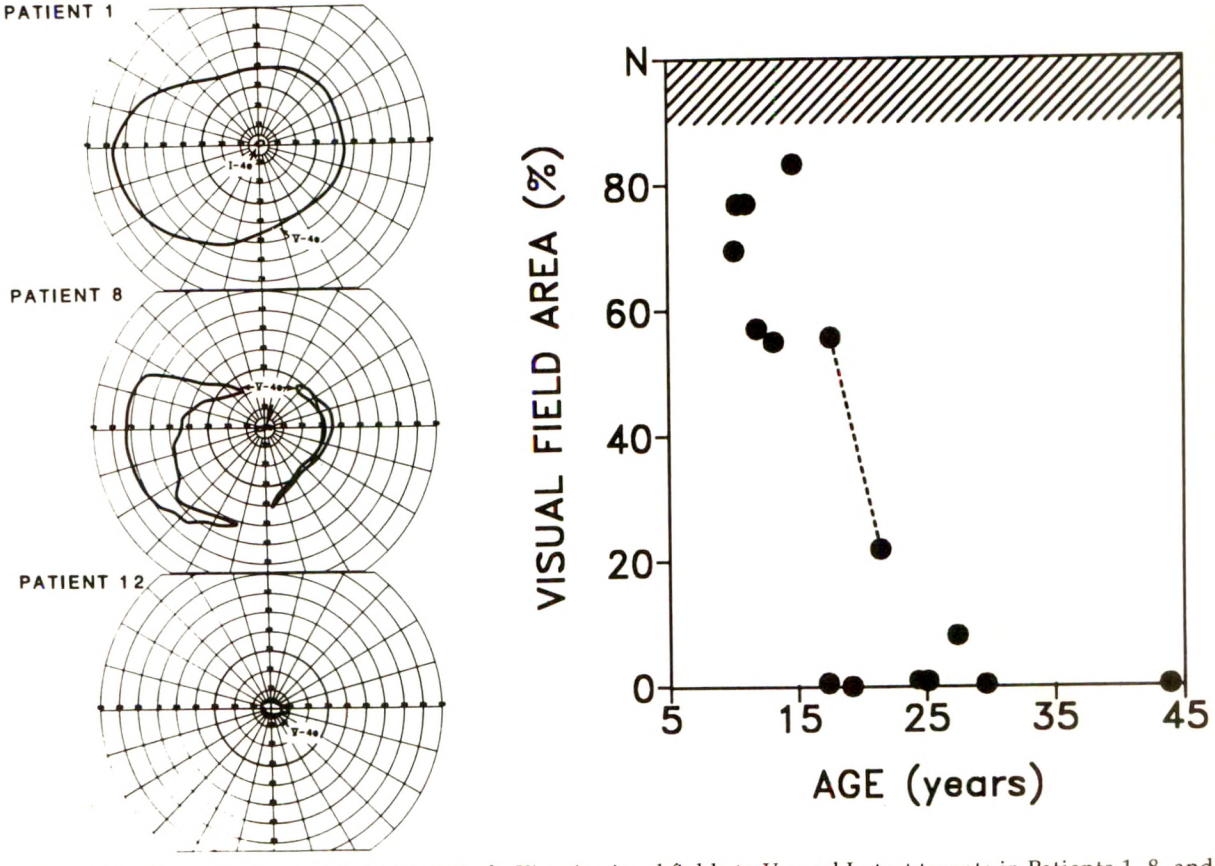

Fig. 1 (Jacobson, Borruat, and Apáthy). Left, Kinetic visual fields to V_{4e} and I_{4e} test targets in Patients 1, 8, and 12. Right, Visual field area vs age. The average of the results from the two eyes are plotted because the fields showed no major interocular asymmetries. Two results for one patient, separated by almost four years, are connected by a dotted line. Mean normal field area (N = 22[13]) is taken as 100% (N); hatched area represents 2 S.D. below the mean normal.

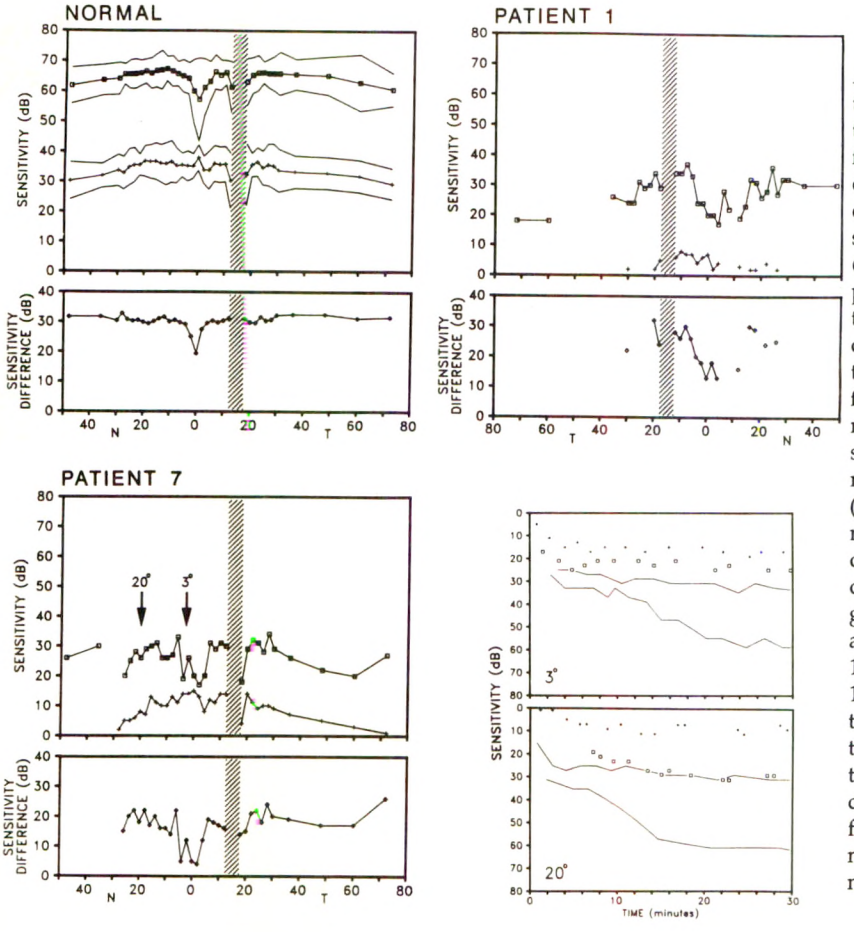

Fig. 2 (Jacobson, Borruat, and Apáthy). Top left, Dark-adapted two-color static perimetric profile tests along the horizontal meridian for normal subjects. Top right, Left eye of Patient 1. Bottom left, Right eye of Patient 7. Upper panels, Sensitivities to 500-nm (square) and 650-nm (plus sign) stimuli. Lower panels, Sensitivity differences between the two colors. The photoreceptor that mediates detection of the stimulus can be determined from the sensitivity differences: rod mediation (rods detect both colors; sensitivity difference, ≥ 28 dB); mixed rod and cone mediation (rods detect 500 nm and cones 650 nm; difference, 13 to 27 dB); and cone mediation (cones detect both colors; difference, ≤ 12 dB). In the graphs of normal subjects, symbols are the mean results (N = 10; ages, 13 to 54 years) and solid lines are ± 1 S.D. Hatched bars indicate location of physiologic blind spot. Bottom right, Two-color dark adaptometry results at two loci, 3 degrees and 20 degrees in the nasal field of Patient 7; solid lines connect data points from a 24-year-old normal subject.

units reduced. At the foveal locus in Patient 1, sensitivity to 650 nm (representing cone function) was reduced by about 2.5 log units compared with normal cone sensitivity to 650 nm at this locus measured during the cone plateau of dark adaptation (mean, 34 dB; S.D., 7 dB; N = 4).

The pattern of results of the dark-adapted two-color profile in Patient 7, a 15-year-old girl, was similar to that in Patient 1 except that there was measurable function between 30 and 60 degrees in the temporal field. In this region and further nasally and temporally, sensitivities were 3.5 to 4 log units reduced at 500 nm, and there was mixed rod- and cone-mediated function. Cone sensitivity (that is, 650-nm sensitivity compared with normal during the cone plateau of dark adaptation) was reduced between about 1.5 and 2.0 log units across the retina sampled, including the foveal locus. Two-color dark adaptometry was performed at 3 degrees and 20 degrees nasal to fixation in this patient (Fig. 2). In contrast to the representative normal function, which shows the typical cone and rod branches, the patient's results at 3 degrees nasally indicated that there was only cone function (there was no rod-cone break, and sensitivity at 30 minutes after onset of dark adaptation had not increased beyond what was measured after a few minutes). The patient's cone sensitivity was impaired by almost 1.5 log units; rod sensitivity was impaired by at least 4 log units. At 20 degrees nasally, there was evidence of a rod branch to the patient's dark adaptation function (sensitivity differences between 500 and 650 nm were greater at 30 minutes than at eight to ten minutes after the bleaching light exposure); at this locus, cone sensitivity was reduced by about 1.5 log units and rod sensitivity by about 3 log units. There was no evidence of any prolongation of rod dark-adaptation in this patient and in the others tested with dark adaptometry such as has been found in some patients with retinitis pigmentosa.[19,20]

Patients 1, 2, and 7 were also tested with two-color dark-adapted perimetry using the full-field test. The mean rod sensitivity losses determined from these 75 measurements at 500 nm, dark-adapted, were 4.2 (S.D., 0.5), 4.4 (S.D., 0.55), and 4.1 (S.D., 0.48) log units for Patients 1, 2, and 7, respectively. Mean cone sensitivity losses based on 650 nm, dark-adapted (compared with sensitivity to 650 nm at the cone plateau in normal subjects) for the same three patients were 2.0 (S.D., 0.4), 1.9 (S.D., 0.3) and 1.6 (S.D., 0.26) log units.

The pattern of rod and cone dysfunction across the visual field of the left eye of Patient 6, a 13-year-old boy with considerably more function by perimetry and electroretinography than the other young patients, is shown in Figure 3. The results of two-color dark-adapted perimetry indicated that sensitivity was rod-mediated at most of the test loci with measurable function, with the exception of the foveal locus and some nasal field loci. Rod sensitivity was reduced by about 2 to 3 log units in most of the mid and far peripheral field and was diminished by about 4 to 5 log units more centrally and superiorly. Cone sensitivity with light-adapted perimetry appeared to follow a similar regional pattern with the least severe reductions (about 0.5 to 1.0 log unit) in the mid and far periphery, greater severity superiorly (1.0 to 1.5 log units), and the most severe effects (>1.5 log units) with scotomatous areas in the central field. Surviving patches of impaired rod and cone sensitivity were present centrally (Fig. 4), and visual acuity was 20/80. Mean rod sensitivity loss for the full-field test was 3.5 (S.D., 1.0) log units. Cone sensitivity loss for the 650-nm stimulus in the dark-adapted state could not be calculated because most loci were rod-mediated. For the 600-nm stimulus in the light-adapted state, mean cone sensitivity loss was 1.2 (S.D., 0.55) log units.

The relationship of rod to cone sensitivity loss at all extrafoveal loci with measurable function in Patient 6 is also shown in Figure 3; there is a highly significant correlation ($r = 0.68$, $P < .0001$). Because neither rod nor cone sensitivity loss is clearly the independent variable, ordinary regression methods cannot be used to quantify the relationship between the variables. The estimate of the slope of rod sensitivity loss onto cone sensitivity loss generated using the method of grouping[21,22] was 1.30 (95% confidence limits, 0.9 to 1.7) with an intercept of 18.5.

The intercept, although it is an extrapolation beyond the range of the data at this stage of the patient's condition (Fig. 3), may help determine which photoreceptor system first shows measurable sensitivity loss in this retinopathy. Confidence intervals for the intercept were deter-

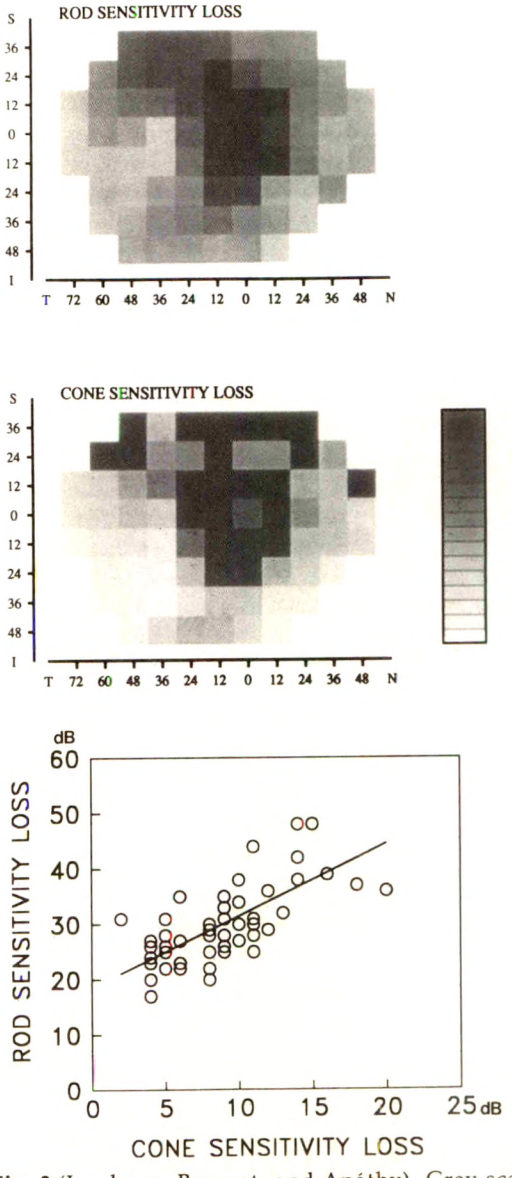

Fig. 3 (Jacobson, Borruat, and Apáthy). Gray scale maps of rod (top) and cone (middle) sensitivity losses throughout the visual field of the left eye of Patient 6. Gray scales have 16 levels of gray, ranging from 0 to 54 dB for rods and 0 to 30 dB for cones; black indicates no detection of the stimulus. The relation of rod and cone sensitivity losses for all loci with measurable function to both stimuli (bottom) is shown; there is a significant correlation ($r = 0.68$, $P < .0001$).

mined as follows. The variability associated with rod and cone sensitivity measurements was estimated from replicate measures; these were pooled to obtain a root-mean-square error in the same way as the short-term fluctuation is obtained in more conventional automated perimetry.[23] The error associated with these measurements was 1.52 for rod sensitivity loss and 1.41 for cone sensitivity loss. These estimates of error were then applied to two other regression models that account for measurement error,[24] yielding slopes with confidence intervals ranging from 0.9 to 2.8. Confidence limits associated with the two regression estimates on the y-intercept (the rod sensitivity loss at zero cone sensitivity loss) were as low as 5 dB and as high as 22 dB; the range is wide, but it does exclude zero. Thus, there may be significant rod sensitivity loss before cone sensitivity losses are measurable.

Bull's-eye lesions and geographic atrophy of the retinal pigment epithelium and choriocapillaris are two patterns of fundus change that have been described in the macula of patients with the Bardet-Biedl syndrome[3] as well as other retinopathies.[25] There were five patients with bull's-eye lesions and one with geographic atrophy in this study. Examples of these two fundus appearances in patients with advanced disease (that is, those with considerable peripheral visual field loss), Patients 10 and 16, are shown in Figure 4 with results of fundus kinetic perimetry and dark-adapted static perimetry. In Patient 10, there is only a small ovoid island of residual function located in the center of the bull's-eye lesion. The dark-adapted static profile indicates that there are only cone-mediated loci in this island. Three other patients with bull's-eye lesions were examined with these perimetric techniques and essentially the same results as those in Patient 10 were found.

In Patient 16, the area corresponding to the geographic atrophy was almost entirely scotomatous except for a fixation locus located in a small patch of pigmented retina within the atrophic lesion. Some functional retina was measurable surrounding the atrophy and into the temporal retina, where a second fixation locus was present. The dark-adapted static profile, with the patient using the more central retinal fixation locus, shows severely impaired cone-mediated function at and near fixation, and rod-mediated function between fixation and the optic disk and on the temporal retinal side of the geographic atrophy. The two different macular lesions in the Bardet-Biedl patients are therefore associated with two different patterns of visual function.

Although younger Bardet-Biedl patients may not show well-defined macular lesions, the patterns of rod and cone sensitivity in their central fields, as illustrated in Figure 4, appear to be less severe stages of the dysfunction found in the advanced patients. Dark-adapted two-color profiles across the central 60 degrees are shown for Patients 2 and 6, two young patients with relatively full visual fields and no obvious macular lesions. The profile in Patient 2 (Fig. 4), which is similar to those in Patients 1 and 7 (Fig. 2), shows cone-mediated function at fixation and mixed-mediated and rod-mediated function with greater eccentricity. The profile in Patient 6 (Fig. 4) shows only severely impaired cone function at fixation and a contiguous area of rod-mediated function between fixation and the optic disk (because of the sampling of the 12-degree grid of the full-field test, this patch of rod function was not detected and therefore is not shown in Figure 3). Beyond a region of severe dysfunction and scotomas to the nasal field side of fixation, rod-mediated function is again measurable. Further loss of function from either of the two patterns represented by the data of Patients 2 and 6 could lead to the patterns found in Patients 10 and 16.

Visual function in the residual central island of Patient 14 differed from the patterns in the other patients studied. Patient 14 was also unusual because of complaints of long-standing photosensitivity and a visual acuity of 20/60 at 31 years of age. With fundus kinetic perimetry, there was a relatively large circular central island with a diameter of about 20 to 25 degrees. Dark-adapted static profiles (Fig. 5, left) indicated that there was almost normal rod-mediated sensitivity near fixation but a precipitous decline in sensitivity beyond an eccentricity of 10 degrees. The rod mediation at all but the fixation locus precluded determination of cone sensitivity in this region with dark-adapted perimetry. Light-adapted sensitivity to 600 nm showed that there was only cone function at three loci near fixation and the sensitivity levels were reduced.

This pattern of rod and cone function within the central island of Patient 14 is not only different from those in the other Bardet-Biedl patients but is also unlike patterns in advanced stages of typical retinitis pigmentosa.[14] For example, the results from a 31-year-old woman with simplex retinitis pigmentosa (Fig. 5, middle) and 20/20 visual acuity were like those in

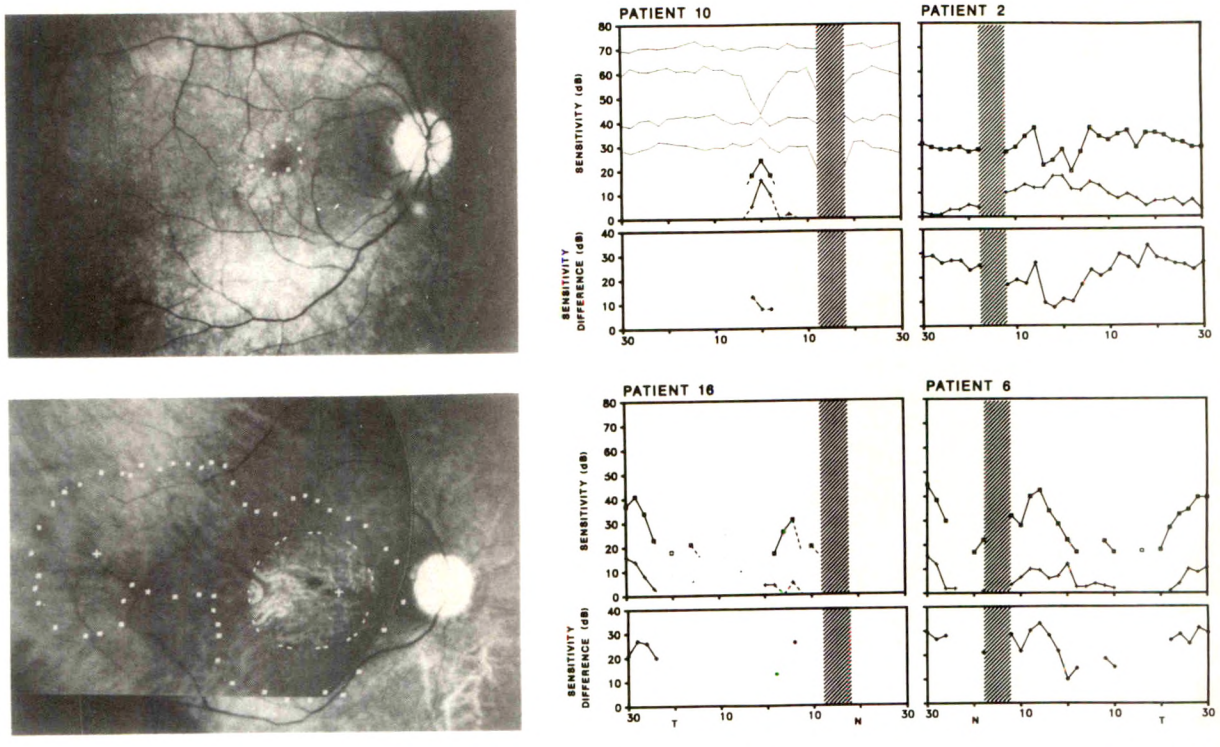

Fig. 4 (Jacobson, Borruat, and Apáthy). Kinetic fundus perimetry (V_{4e} test target) of the residual island of vision superimposed on a fundus photograph of the right eyes of Patient 10 (top left) and Patient 16 (bottom left). Small white squares define boundary of vision; the area of geographic atrophy (within double dashes) was mostly scotomatous. Plus signs indicate the two fixation loci. Dark-adapted two-color static perimetric profiles across the central 60 degrees in the right eyes of Patient 10 (top middle) and Patient 16 (bottom middle); and the left eyes of Patient 2 (top right) and Patient 6 (bottom right). Upper panels, Results with 500-nm (square) and 650-nm (plus sign) stimuli. Lower panels, Sensitivity differences between the two colors. Normal limits (± 1 S.D. from the mean) for sensitivities to the 500-nm (upper set of dotted lines) and 650-nm (lower set) stimuli are shown in the graphs of Patient 10.

Patient 14 in that there was no measurable peripheral field but excellent central rod-mediated sensitivity with an abrupt decline in function beyond an eccentricity of 10 degrees. Unlike Patient 14, however, this patient had nearly normal cone sensitivity throughout the same region wherein there is excellent rod sensitivity. A 47-year-old man with multiplex retinitis pigmentosa (Fig. 5, right) and 20/60 visual acuity, resembled Patient 14 in that he also had no measurable peripheral visual function, the same level of visual acuity, and a similar static perimetric profile with the 600-nm stimulus in the light-adapted state. But the dark-adapted profiles of this retinitis pigmentosa patient and Patient 14 differed remarkably. The only function measurable in this retinitis pigmentosa patient under dark-adapted conditions was the reduced cone sensitivity; there was no detectable rod function in the central island.

Case Report

A 45-year-old woman, sister of Patient 16, had no visual complaints but was told on a routine eye examination of an unusual macular appearance in both eyes. She was obese her entire life (current weight, about 250 lbs.) but was of normal intelligence and had no polydactyly, renal disease, or other stigmata of the Bardet-Biedl syndrome. There was no exposure to known retinal toxins. Best-corrected visual acuity was R.E.: 20/25 (−0.50) and L.E.: 20/30 (plano). Results of Goldmann kinetic perimetry with V_{4e} and I_{4e} test targets were normal.

Full-field electroretinograms from the right eye of this patient are shown in Figure 6; there was no major asymmetry between the recordings from the two eyes.[13] There was reduced amplitude of the rod signal (125 μV vs mean

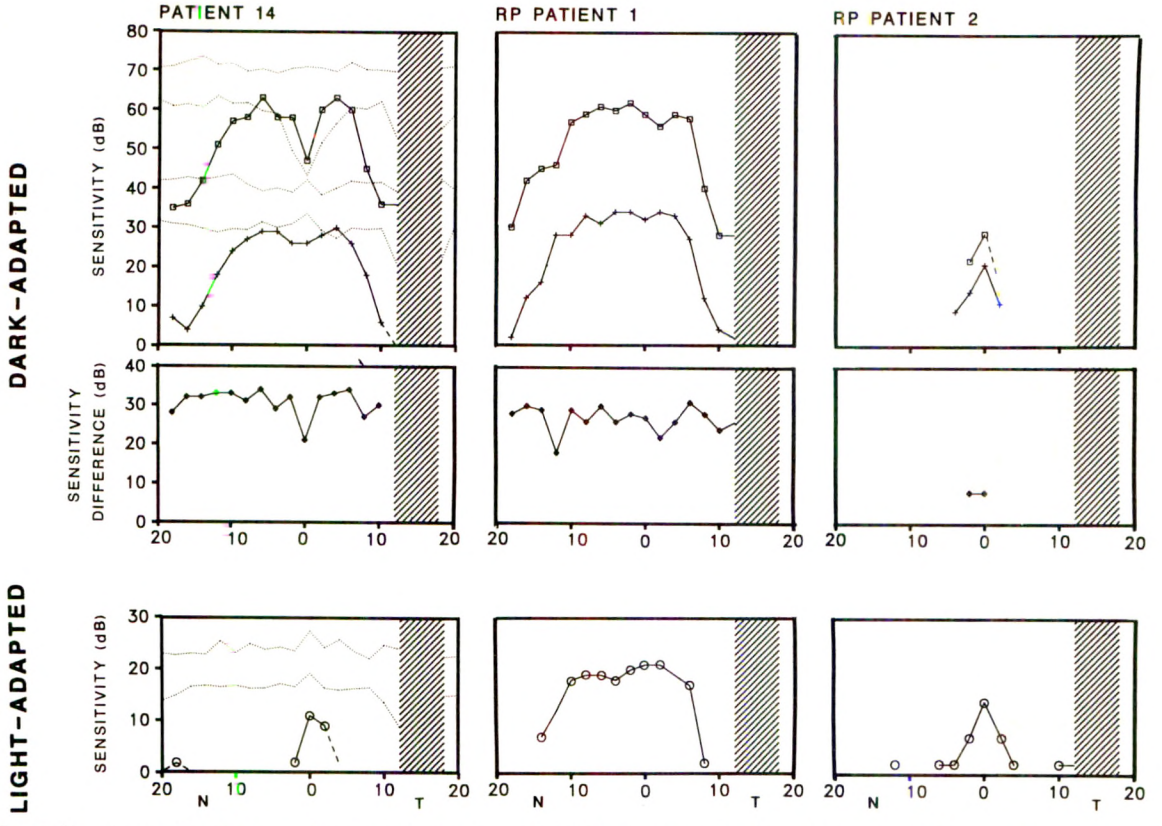

Fig. 5 (Jacobson, Borruat, and Apáthy). Dark- and light-adapted static perimetric profiles in the central 40 degrees of the right eyes of Patient 14 (left), a 31-year-old woman with simplex retinitis pigmentosa (retinitis pigmentosa Patient 1, middle), and a 47-year-old man with multiplex retinitis pigmentosa (retinitis pigmentosa Patient 2, right). Upper panels, Results with 500-nm (square) and 650-nm (plus sign) stimuli, dark-adapted; middle panels, sensitivity differences between these two colors; lower panels, results with 600-nm stimulus on a 10-cd/m^2 white background light. Normal limits (± 1 S.D. from the mean) are shown in the graphs of Patient 14.

normal result of 291.9 μV; S.D., 52.4 μV; N = 22[13]) and delayed implicit time (92 msec vs normal mean, 76.3 msec; S.D., 4.6 msec); the dark-adapted cone signal (digitally subtracted result of the waveforms to scotopically matched blue and red stimuli) was normal in amplitude (115 μV vs normal mean, 160.6 μV; S.D., 48.5 μV) but delayed in implicit time (54 msec vs normal mean, 45.9 msec; S.D., 2.4 msec); and cone flicker electroretinograms were also normal in amplitude (60 μV vs normal mean, 94.5 μV; S.D., 27.8 μV) but delayed in timing (32 msec vs normal mean, 27 msec; S.D., 1 msec). In the voltage-log intensity relationship for the rod electroretinogram (Fig. 6), the Naka-Rushton parameters[26] were as follows: amplitude at response saturation (Vmax) was 162 μV, which is reduced more than 2 S.D. below the normal mean result (mean, 400 μV; S.D., 63 μV; N = 37[9]); the stimulus intensity at one-half Vmax (K) was −1.47, which is between 1 and 2 S.D. of normal (mean, −1.76; S.D., 0.16; N = 37); and the exponent "n" was 0.9 (normal mean, 0.87; S.D., 0.12[9]). To test the hypothesis that this patient's electroretinographic abnormalities may represent the findings in all carriers of this autosomal recessively inherited retinopathy, one parent (in each case, the mother) of two other Bardet-Biedl patients (Patients 6 and 14) was tested with the same technique. All electroretinographic features were normal in these two women.

A focal yellow-white central retinal lesion (Fig. 6), the only abnormality in the eye examination in the sister of Patient 16, was present in both eyes and appeared almost like the lesions

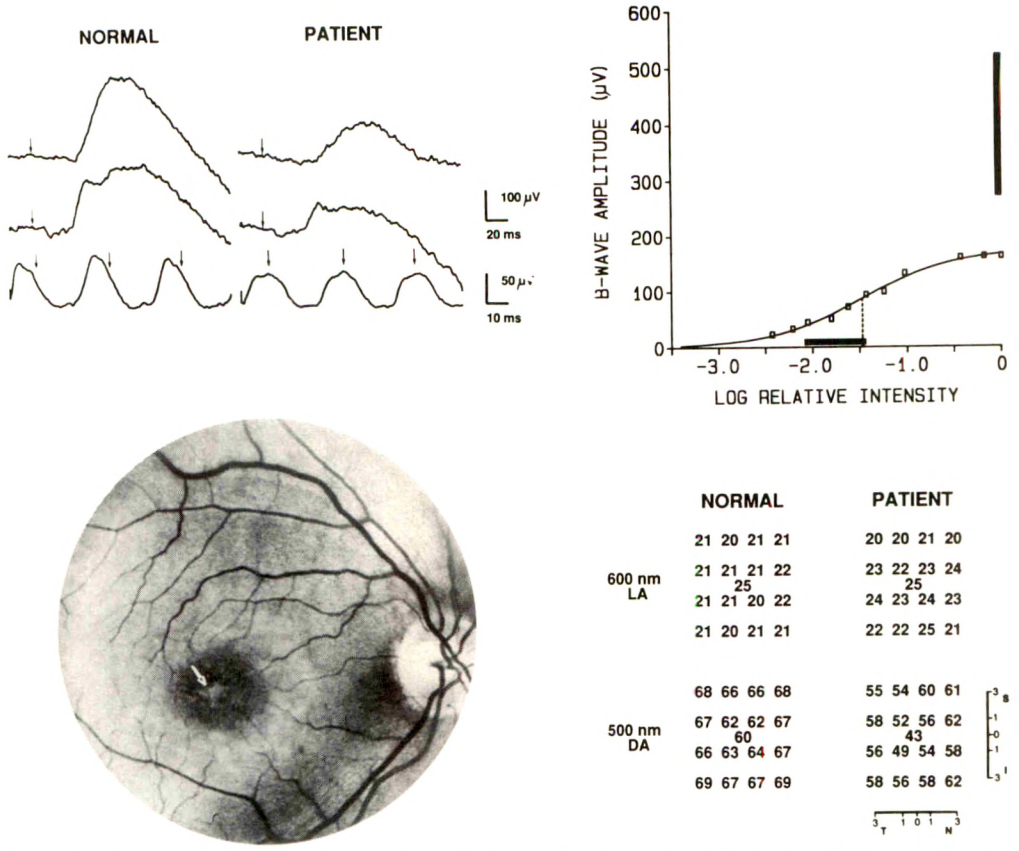

Fig. 6 (Jacobson, Borruat, and Apáthy). Top left, Electroretinograms from a 34-year-old normal subject and the 41-year-old sister of Patient 16 to dim blue flashes of light, dark-adapted; scotopically matched red flashes; and 29-Hz white flickering light. Arrows indicate stimulus onset. Upper calibration bars are for the two sets of dark-adapted responses, and the lower calibration bars are for the responses to flicker. Top right, Relation of b-wave amplitude to relative stimulus intensity for a series of blue light flashes, dark-adapted. Normal mean results ± 2 S.D. (N = 37[9]) are shown as solid bars for maximum amplitude (ordinate) and for K, log intensity at one-half maximum amplitude (abscissa). Bottom left, Fundus photograph of the central retinal region of the right eye of this patient; white arrow indicates pigmentary disturbance. Bottom right, Sensitivities in the central 6 degrees of visual field of the left eye to the 600-nm stimulus in the light-adapted state, and the 500-nm stimulus in the dark-adapted state, in normal subjects (mean, ten subjects) and in the left eye of the patient.

described in butterfly-shaped pigment dystrophy of the fovea.[27] Dark- and light-adapted static perimetry was performed with a full-field test and a macula test. The full-field test showed that 35 of the 75 loci had rod sensitivity >2 S.D. below the mean normal; all rod sensitivity losses were in the range of 0.6 to 1.2 log units. With the macula test (Fig. 6), dark-adapted sensitivities with the 500-nm stimulus were reduced (>2 S.D. below the mean normal at each locus) by about 1 log unit across the area tested. On the full-field test with the 600-nm stimulus in the light-adapted state, there were only two loci with abnormal cone sensitivities; the macula test results were normal.

Discussion

The retinal degeneration in this series of patients with the Bardet-Biedl syndrome led to severe central and peripheral visual dysfunction by the second and third decades of life and affected both rod- and cone-mediated function throughout the retina. Visual acuities were abnormal in all patients, but the data did not suggest a direct relationship of visual acuity with age. Kinetic perimetry disclosed that the visual field area was abnormal by age 10 years. As early as age 17 years and certainly by age 24 years, there was rarely more than a central

island of vision remaining. In two patients, midperipheral scotomas separated central and far peripheral islands, which suggests that this regional pattern may precede the complete loss of peripheral retinal function. Like most of the published electroretinographic results,[1,3-5] there were either no detectable signals or only cone electroretinograms were recordable. An electroretinographic pattern in which cones are worse than rods, such as has been reported in one Bardet-Biedl patient,[2] was not present in any of our patients.

Dark- and light-adapted static perimetry in the young Bardet-Biedl patients with measurable peripheral visual field not only confirmed the electroretinographic finding of decreased rod- and cone-mediated function across the retina but also showed that the patterns of dysfunction in this syndrome do not conform exactly to either of the two subtypes of typical retinitis pigmentosa that have been defined with this technique.[8,28,29] In type 1 or diffuse retinitis pigmentosa, there is early and severe loss of rod sensitivity almost uniformly across the retina but a regional variation of cone sensitivity.[8,28,29] Patients 1, 2, and 7 had from 3 to more than 4 log units of rod sensitivity loss diffusely across the visual field, which are findings similar to those in type 1 retinitis pigmentosa. Although Patient 6 showed a greater range of rod sensitivity losses (from 1.5 to more than 4 log units), this finding still conforms to at least one definition of this subtype.[29] The severity of the cone sensitivity loss centrally and throughout the periphery in these Bardet-Biedl patients, however, is not a feature of type 1 retinitis pigmentosa. In type 2 or regionalized retinitis pigmentosa, rod and cone sensitivity losses occur together and there is variation in the severity of loss across the retina, some regions being profoundly abnormal whereas other regions are far less affected or even normal.[8,28,29] There was combined loss of both rod and cone sensitivity in the four young Bardet-Biedl patients, but no retinal zones were as relatively spared as in type 2 retinitis pigmentosa.

Because macular dysfunction occurs early in the course of the Bardet-Biedl retinopathy and in cone-rod dystrophy, it has been suggested that they are the same type of retinal degeneration.[30] As indicated, electroretinographic measures of retinal function in our Bardet-Biedl patients were not consistent with the diagnosis of cone-rod dystrophy. Furthermore, the perimetric patterns of peripheral rod and cone dysfunction in the four young patients were unlike any of the patterns recently defined with this technique in autosomal-recessive or simplex/multiplex cone-rod dystrophy.[9]

The patterns of rod and cone sensitivities in the peripheral visual field of the young patients provided no strong evidence for more than one phenotype in the retinopathy of the Bardet-Biedl syndrome, but central visual function was remarkably different among the patients with more advanced disease. In three young patients (Patients 1, 2, and 7), the data were similar; the greater range of rod and cone sensitivities measured in the fourth patient (Patient 6) could represent an earlier stage of the same retinopathy. In patients with more advanced disease, the bull's-eye lesions and the geographic atrophy of the retinal pigment epithelium were not only distinct by fundus appearance but also by functional testing, and the differences cannot be explained as stages of the same maculopathy.[3] The patterns of rod and cone sensitivity in the central visual field of the younger patients seem to represent earlier and milder expressions of these two phenotypes of macular change in advanced patients.

Another phenotype of abnormal macular function in this syndrome was found in the data of Patient 14. The pattern of preserved rod sensitivity but severely impaired cone sensitivity cannot be explained as a later stage of the retinopathy in our younger patients nor an earlier stage of the pattern of dysfunction found in geographic atrophy. It is conceivable that the condition of Patient 14 could progress to only a small cone-mediated central island of function; such a pattern would be indistinguishable from that in advanced patients with bull's-eye lesions. The results of Patient 14 also differ from those of patients with advanced stages of either type 1 or type 2 retinitis pigmentosa.[14] The pattern has some similarities to that in a type of cone-rod dystrophy we recently described[9] that also shows retained central rod function and severely abnormal cone function. Unlike Patient 14, however, patients with this type of cone-rod dystrophy had a recordable rod electroretinogram, no measurable cone function by electroretinography or perimetry, visual acuity worse than 20/200, and greater impairment of central rod sensitivity but islands of peripheral rod sensitivity.[9] The lack of measurable peripheral visual function in Patient 14 precludes our knowing whether his results represent the advanced stage of a widespread cone-worse-than-rod dysfunctional pattern[2] or are simply

another but more unusual expression of the maculopathy in this syndrome.

The type of photoreceptor-mediated dysfunction that is the earliest manifestation of the Bardet-Biedl retinopathy (rod dysfunction, cone dysfunction, or both) is not known. The lack of such knowledge is probably the result of the following: the syndrome is relatively rare, there is an early onset and rapid progression of retinal dysfunction, and it is difficult to obtain reliable psychophysical measurements of retinal function in children, especially because many afflicted children have subnormal intelligence. Three previous studies,[6,7,31] however, have reported interesting results in children with the syndrome. Dark-adapted sensitivities to a 10-degree blue stimulus 20 degrees from fixation in afflicted children were reported to show as much as 3 log units of rod sensitivity loss as early as 2 years of age; visual acuity, the only measure of cone function in these patients, was only mildly abnormal in the first decade of life.[7] An 8-year-old Bardet-Biedl patient with macular dysfunction had normal rod electroretinogram amplitude to dim stimuli but a reduced electroretinogram to suprathreshold stimulation; cone electroretinogram amplitudes were normal but timing was delayed.[6] These findings were interpreted as those of a widespread cone-rod degeneration, but could as well represent a rod maximum amplitude (Vmax) reduction and a cone timing delay secondary to the rod amplitude loss.[32] A morphologic study of the donor retina from a 4-year-old child with this syndrome showed both photoreceptors affected outside the macula and severe degenerative changes in the macula.[31]

Data from the two least-affected patients in this study suggest that the rod photoreceptor system may be more affected early in the disease. First, the electroretinographic and perimetric results of Patient 6 show that the rod system can be severely affected when the cone system is far less so. The extrapolation to zero of the relationship between rod and cone sensitivity losses in this patient's perimetric data suggests that near the origin of the graph there could be greater rod sensitivity loss for a given cone sensitivity loss (Fig. 3). Second, the most pronounced abnormality in the asymptomatic sister of Patient 16 was rod-mediated dysfunction in peripheral and central retina. The only evidence for cone-mediated dysfunction was the mildly reduced visual acuity and the timing delay in the cone electroretinogram; the latter finding, however, could be related to the rod electroretinogram amplitude loss.[32] It is not known whether this patient's retinopathy was a minimal expression of the homozygous state or a detectable expression of the heterozygous state of an autosomal-recessive disease, such as has been reported to occur in animals.[33]

Acknowledgment

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Indications for and Outcomes of Repeat Penetrating Keratoplasty

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We reviewed data on 150 repeat corneal transplants performed between 1983 and 1988 at Wills Eye Hospital. Minimal postoperative follow-up was six months. The most common diagnoses before regraft were pseudophakic bullous keratopathy (29 of 150), aphakic bullous keratopathy (28 of 150), Fuchs' dystrophy (21 of 150), failed graft (17 of 150), and keratoconus (14 of 150). Herpes simplex keratitis, interstitial keratitis, chemical burns, traumatic scars, and corneal dystrophies accounted for most of the remaining regrafts. Of the 150 regrafts, 39 (26%) failed during the study period. Almost half of the regraft failures occurred within six months, and over four fifths occurred within 18 months. Of the 111 eyes with clear grafts, final visual acuity data were available for 68 eyes (minimal follow-up, two years; mean, 3.3 years). A best-corrected visual acuity of 20/20 to 20/40 (22 of 68) or 20/50 to 20/100 (27 of 68) was achieved in most patients.

REPEAT CORNEAL TRANSPLANTATION continues to be one of the leading indications for penetrating keratoplasty.[1-5] Despite many advances in pharmacology, instrumentation, and technique over the years, approximately 10% of the grafts performed at our institution between 1983 and 1986 were repeat grafts.[1]

We reviewed the clinical indications and outcomes of 150 repeat penetrating keratoplasties performed by one of three corneal surgeons at our institution over the six-year period from 1983 to 1988. These data were compared with the clinical indications for all 2,299 penetrating keratoplasties performed at our institution during the same period. Reasons for primary graft failure and regraft failure were examined. Regrafts for pseudophakic bullous keratopathy were evaluated in relation to the type of intraocular lens, disposition of the intraocular lens at the time of transplant, and graft clarity. Indications for the initial corneal graft and graft clarity of eyes that underwent multiple regrafts were also reviewed. Visual acuity data for eyes with clear grafts and a minimum of two years of follow-up were evaluated.

Material and Methods

We reviewed the hospital and private office charts of all private patients who underwent repeat penetrating keratoplasty by one of three corneal surgeons at Wills Eye Hospital between Jan. 1, 1983, and Dec. 31, 1988. Information including the patient's gender and age, dates of previous and most recent penetrating keratoplasties, clinical diagnosis before the initial graft, reason for the graft failure, associated procedures, and total number of grafts performed was reviewed. When more than one graft was performed on the same eye during this period, data from the most recent graft were used. We obtained data on best-corrected visual acuity and graft clarity before the last regraft and at six months (± one month), 12 months (± two months), 18 months (± three months), two years (± three months), and at three, four, five, and six years (± four months) after the regraft. Every patient had at least six months of follow-up.

Clinical indications for the previous penetrating keratoplasty were divided into 18 categories (Table 1). When three or more grafts had

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TABLE 1
PREVIOUS DIAGNOSES FOR REPEAT PENETRATING KERATOPLASTIES

PREVIOUS DIAGNOSIS	1983	1984	1985	1986	1987	1988	TOTAL
Pseudophakic bullous keratopathy	2	4	3	6	6	8	29 (19.3%)
Aphakic bullous keratopathy	3	4	4	5	7	5	28 (18.7%)
Fuch's dystrophy	2	3	7	4	0	5	21 (14.0%)
Multiple regraft	2	3	1	6	3	2	17 (11.3%)
Keratoconus	3	1	4	3	3	0	14 (9.3%)
Herpes simplex virus	0	0	0	3	3	2	8 (5.3%)
Interstitial keratitis	1	0	2	1	1	1	6 (4.0%)
Trauma	0	0	0	1	2	2	5 (3.3%)
Corneal dystrophy	0	3	1	1	0	0	5 (3.3%)
Chemical burn	1	2	0	0	1	1	5 (3.3%)
Ulcer	0	0	1	1	1	0	3 (2.0%)
Edema	0	1	0	0	0	1	2 (1.3%)
Degeneration	0	0	0	0	1	1	2 (1.3%)
Herpes zoster virus	0	0	0	1	0	0	1 (0.7%)
Aniridia	0	0	0	1	0	0	1 (0.7%)
Congenital glaucoma	0	1	0	0	0	0	1 (0.7%)
Sclerocornea	0	1	0	0	0	0	1 (0.7%)
Vascularization	1	0	0	0	0	0	1 (0.7%)
Total	15	23	23	33	28	28	150 (100.0%)

been performed on one eye, it was classified as a multiple regraft, and information from the last regraft was used. Two cases were categorized as corneal edema because a more specific diagnosis could not be determined. The two major reasons for graft failure were allograft rejection and endothelial failure without clinical evidence of allograft rejection. Failure of unknown cause was listed when the patient was first seen at Wills Eye Hospital with a failed graft for which we were unable to determine the cause. Best-corrected visual acuity data were categorized as follows: 20/20 to 20/40, 20/50 to 20/100, 20/200 to 20/400, counting fingers, hand motions, light perception, and no light perception. Graft clarity was recorded as clear or opaque. Any graft that was not clear was classified as opaque. In cases of pseudophakic bullous keratopathy, the type of intraocular lens and its disposition were noted. When additional information was needed, referring physicians were contacted and pathology reports were reviewed.

Results

Between 1983 and 1988, 233 of 2,299 (10%) penetrating keratoplasties performed at Wills Eye Hospital were regrafts.[1] Of these 233 regrafts, 165 were performed by three corneal surgeons (E.J.C., J.J.A., and P.R.L.). Of the 165 regrafts, 150 (91%) had follow-up data for a minimum of six months. An average of 25 regrafts were performed each year, ranging from 15 in 1983 to 33 in 1986 (Table 1). The average age of patients undergoing repeat corneal transplant was 64.2 years, ranging from 58.9 years in 1983 to 67.6 years in 1988. Almost twice as many patients were women (98) as men (52).

Pseudophakic bullous keratopathy and aphakic bullous keratopathy were the most common previous clinical diagnoses of the eyes requiring regrafts, accounting for 29 (19%) and 28 (19%) cases, respectively. Other previous diagnoses of patients who required repeat corneal transplant were Fuchs' dystrophy (21 of 150, 14%), multiple regraft (17 of 150, 11%), keratoconus (14 of 150, 9%), and herpes simplex virus keratitis (eight of 150, 5%). Over the six-year study period, the percentage of repeat penetrating keratoplasties initially performed for pseudophakic bullous keratopathy was noted to increase from 13% (two of 15) in 1983 to 29% (eight of 28) in 1988. This trend, however, was not statistically significant. No regrafts were performed for herpes simplex virus keratitis during the first three years of the study, whereas either two or three such regrafts were performed each of the last three years of the study (Table 1).

Multiple repeat penetrating keratoplasties were performed on 17 eyes. The initial clinical diagnoses for these 17 eyes were pseudophakic bullous keratopathy (six of 17, 35%), aphakic bullous keratopathy (six of 17, 35%), Fuchs' dystrophy (two of 17, 12%), and one each for keratoconus, herpes simplex virus keratitis, and corneal edema secondary to congenital glaucoma (6%). Clinical indications for all penetrating keratoplasties performed at our institution between 1983 and 1988[1] and repeat penetrating keratoplasties in this study and their original diagnoses are shown in Table 2. The clinical indications for initial corneal transplants at our institution and repeat corneal transplants by three of us (E.J.C., J.J.A., and

TABLE 2
ALL CORNEAL GRAFTS AT WILLS EYE HOSPITAL COMPARED WITH CORNEAL REGRAFTS STUDIED

DIAGNOSIS	TOTAL NO. OF GRAFTS FROM 1983 TO 1988	REPEAT GRAFTS BY ORIGINAL DIAGNOSIS
Pseudophakic bullous keratopathy	526 (22.9%)	35 (23.3%)
Aphakic bullous keratopathy	331 (14.4%)	34 (22.7%)
Fuchs' dystrophy	375 (16.3%)	23 (15.3%)
Repeat grafts	233 (10.1%)	—
Keratoconus	348 (15.1%)	15 (10.0%)
Virus	101 (4.4%)	10 (6.7%)
Interstitial keratitis	88 (3.8%)	6 (4.0%)
Trauma	58 (2.5%)	5 (3.3%)
Dystrophy	39 (1.7%)	5 (3.3%)
Chemical burn	11 (0.5%)	5 (3.3%)
Ulcer	58 (2.5%)	3 (2.0%)
Congenital anomaly	9 (0.4%)	4 (2.7%)
Degeneration	11 (0.5%)	3 (2.0%)
Edema	28 (1.2%)	2 (1.3%)
Unknown scarring	49 (2.1%)	0 (0.0%)
Unknown	21 (0.9%)	0 (0.0%)
Miscellaneous	13 (0.6%)	0 (0.0%)
Total	2,299 (100.0%)	150 (100.0%)

P.R.L.) are similar with the exceptions of aphakic bullous keratopathy, keratoconus, and chemical burn. Aphakic bullous keratopathy accounted for only 331 of 2,066 (16%) initial corneal grafts, and for 34 of 150 (23%) of initial diagnoses for repeat and multiple repeat corneal grafts (P = .05). Keratoconus represented 348 of 2,066 (17%) initial corneal transplants and only 15 of 150 (10%) initial diagnoses of repeat and multiple repeat corneal transplants (P = .04) Chemical burns accounted for only 11 of 2,066 (0.5%) of all initial corneal grafts, whereas they accounted for five of 150 (3%) repeat corneal grafts during the same time period (P = .001).

The cause of previous graft failure was determined in 134 of 150 eyes (89%). In the undeterminable cases, the courses were not observed by us, and results of histopathologic examinations were noncontributory. Of the 134 cases for which reasons for graft failure could be determined, 48 (36%) were caused by allograft rejection and 51 (38%) were caused by endothelial failure without evidence of allograft rejection. Other causes of graft failure included scarring (12 of 134, 9%), severe astigmatism (nine of 134, 7%), recurrent herpes simplex virus (five of 134, 4%), recurrent dystrophy (four of 134, 3%), ulceration (four of 134, 3%), and, less commonly, epithelial downgrowth (one of 134, 1%) and wound dehiscence (one of 134, 1%) (Table 3).

The average number of years between the first and second corneal transplant varied depending on the diagnosis, ranging from three years for eyes with pseudophakic bullous keratopathy to 19 years for eyes with keratoconus (Table 4). The time between the first and second transplant in the seven grafts performed for severe astigmatism in patients with keratoconus was even greater, averaging 23 years.

Of the 150 regrafts, 39 (26%) failed during the study period (range, six months to six years; mean, 2.4 years). The most common clinical indications for the previous grafts of the regraft failures were aphakic bullous keratopathy (11 of 39, 28%), pseudophakic bullous keratopathy (eight of 39, 21%), and repeat grafts (seven of 39, 18%) (Table 5). Endothelial failure without evidence of allograft rejection (16 of 39, 41%) and allograft rejection (14 of 39, 36%) were the most common causes for regraft failure. Epithelial downgrowth caused regraft failure in three patients (8%). Almost one half (17 of 39, 44%) of the regrafts failed within the first six months, almost two thirds (25 of 39, 64%) failed within the first year, and over four fifths (32 of 39, 82%) failed within the first 18 months of the regraft. Two patients who eventually returned to our institution with failed regrafts had been lost to follow-up for one and two years. The average age of the regraft at the time of failure was 14.8 months (range, six months to four years) for those failures secondary to endothelial failure and 16.2 months (range, six months to five years) for those secondary to allograft rejection.

Twenty-nine regrafts were performed in patients with pseudophakic bullous keratopathy. Anterior chamber intraocular lenses accounted for 19 lenses (14 Leiske lenses, one Choyce lens, two open loop anterior chamber lenses, and two unspecified anterior chamber lenses), iris-fixated intraocular lenses were present in eight patients (five Copeland lenses, two Binkhorst lenses, and one Sputnik lens), and posterior chamber intraocular lenses were present in two patients. At the time of first corneal trans-

TABLE 3
REASONS FOR PREVIOUS GRAFT FAILURE

PREVIOUS DIAGNOSIS	FAILURE OF UNKNOWN CAUSE	ENDOTHELIAL FAILURE	ALLOGRAFT REJECTION	SEVERE ASTIGMATISM	OTHER	TOTAL
Pseudophakic bullous keratopathy	4	14	9	0	2	29
Aphakic bullous keratopathy	1	11	15	1	0	28
Fuchs' dystrophy	2	8	8	1	2	21
Multiple regraft	1	8	5	0	3	17
Keratoconus	1	0	2	7	4	14
Herpes simplex virus	0	2	2	0	4	8
Interstitial keratitis	0	0	3	0	3	6
Trauma	3	1	1	0	0	5
Corneal dystrophy	1	0	0	0	4	5
Chemical burn	1	2	0	0	2	5
Ulcer	1	0	2	0	0	3
Edema	0	2	0	0	0	2
Degeneration	0	0	0	0	2	2
Others	1	3	1	0	0	5
Total	16 (10.7%)	51 (34.0%)	48 (32.0%)	9 (6.0%)	26 (17.3%)	150 (100%)

plant, only three intraocular lenses were removed (a Leiske lens and two unspecified anterior chamber intraocular lenses) and none were exchanged. At the time of regraft, 11 intraocular lenses were left in the eye, seven were exchanged, and eight were removed. Twenty of these 29 patients (69%) had a minimum of 18 months of follow-up. In patients with at least 18 months of follow-up, grafts remained clear in five of eight patients in whom the intraocular lens was removed or previously removed, one of four patients in whom the intraocular lens was exchanged, and five of eight patients in whom the intraocular lens was left in the eye. Two of the regraft failures after intraocular lens exchange were attributable to endothelial failure and one was secondary to epithelial downgrowth. The three failures that occurred after the intraocular lens was left in the eye at the time of regraft all occurred in eyes with Leiske anterior chamber intraocular lenses.

Six of the multiple regrafts were performed on eyes that had the initial diagnosis of pseudophakic bullous keratopathy; four of these eyes had a minimum follow-up of three years. One eye had a Copeland lens that had been removed at the time of first corneal transplant. One eye

TABLE 4
AVERAGE NUMBER OF YEARS BETWEEN THE FIRST AND SECOND GRAFTS

ORIGINAL DIAGNOSIS	NO. OF EYES	AVERAGE NO. OF YEARS BETWEEN GRAFTS
Keratoconus	14	18.5
Herpes simplex virus	8	8.8
Interstitial keratitis	6	8.7
Fuchs' dystrophy	21	6.3
Aphakic bullous keratopathy	28	3.8
Pseudophakic bullous keratopathy	29	3.3

TABLE 5
FAILED REGRAFTS

PREVIOUS DIAGNOSIS	NO. OF FAILED REGRAFTS
Aphakic bullous keratopathy	11 (28.2%)
Pseudophakic bullous keratopathy	8 (20.5%)
Multiple repeat grafts	7 (17.9%)
Fuchs' dystrophy	3 (7.7%)
Keratoconus	2 (5.1%)
Trauma	2 (5.1%)
Alkali burn	2 (5.1%)
Herpes simplex virus	1 (2.6%)
Interstitial keratitis	1 (2.6%)
Sclerocornea	1 (2.6%)
Aniridia	1 (2.6%)
Total	39 (100.0%)

had a Leiske lens and one eye had an open loop anterior chamber intraocular lens, both of which were removed at the time of regraft. The fourth eye had a Copeland lens exchanged for an open loop anterior chamber intraocular lens at the time of regraft. All four grafts were clear at the end of the study period.

Seventeen of the repeat corneal transplants were performed on eyes that had multiple graft failures. One of the eyes had undergone five grafts, another eye had undergone four grafts, and the 15 other eyes had undergone three grafts. The two eyes with more than three grafts had initial diagnoses of aphakic bullous keratopathy. Seven of the 17 (41%) multiple regrafts failed; five of these cases failed by six months and two failed by one year after regraft. The original diagnoses for the seven failed regrafts were aphakic bullous keratopathy (three eyes), Fuchs' dystrophy (two eyes), corneal edema secondary to congenital glaucoma (one eye), and herpes simplex virus keratitis (one eye). Failure was caused by allograft rejection in two grafts, endothelial failure in two grafts, epithelial downgrowth in two grafts, and intractable glaucoma in another.

Minimal two-year follow-up (range, two to six years; mean, 3.3 years) visual acuity data were available on 90 (60%) eyes. Twenty-two of these eyes had failed grafts. Of the remaining 68 eyes, 22 (32%) had a best-corrected visual acuity of 20/20 to 20/40, 27 (40%) had a best-corrected visual acuity of 20/50 to 20/100, and 14 (21%) had a best-corrected visual acuity of 20/200 to 20/400. Four (6%) eyes had counting fingers visual acuity secondary to a macular hole (one eye), glaucoma (one eye), trauma (one eye), and age-related macular degeneration (one eye). One eye (1%) had hand motions visual acuity secondary to a retinal detachment. In 60 of these 68 eyes (88%), the visual acuity improved at least one visual acuity category from before the last graft, in seven eyes the visual acuity remained in the same category, and the visual acuity in one eye became worse because of a macular hole (Figure).

Discussion

In 1974, Cowden, Kaufman, and Polack[6] reviewed their data on 51 repeat corneal transplants. The initial diagnoses for these regrafts were primarily Fuchs' dystrophy and aphakic bullous keratopathy (80%) and infectious ulcers including herpes and fungus (10%). In 1979, Robinson[7] examined the indications and outcomes of 47 corneal regrafts in 29 eyes. Clinical diagnoses for the initial grafts were primarily Fuchs' dystrophy (six of 29, 21%), bullous keratopathy (six of 29, 21%), keratoconus (five of 29, 17%), aphakic bullous keratopathy (four of 29, 14%), and interstitial keratitis (two of 29, 7%). More recently, in 1988, MacEwen and associates[8] reported the results of 62 repeat grafts performed in 41 eyes between 1977 and 1986. The clinical indications for the initial grafts were herpes simplex virus keratitis (nine of 41, 22%), pseudophakic bullous keratopathy (seven of 41, 17%), aphakic bullous keratopathy (four of 41, 10%), Fuchs' dystrophy (four of 41, 10%), bacterial ulcer (three of 41, 7%), rosacea (three of 41, 7%), scarring (three of 41, 7%), interstitial keratitis (two of 41, 5%), keratoconus (one of 41, 2%), and others (five of 41, 13%).

In our study, pseudophakic bullous keratopathy and aphakic bullous keratopathy accounted for 69 (46%) of the initial diagnoses of all the regrafts. Fuchs' dystrophy, keratoconus, and herpes simplex virus keratitis were the next most common initial diagnoses. The increased percentage of regrafts for pseudophakic bullous keratopathy coincides with the increased number of intraocular lenses being implanted in the United States[9] and also the rise in pseudophakic bullous keratopathy as an indication for primary corneal transplants at our institution.[1] Over the six-year period of this study, aphakic bullous keratopathy continued to be the initial diagnosis of a significant number of regrafts, whereas during the same period it was declining as an indication for primary corneal transplant at our institution.[1] Regrafts in patients with herpes simplex virus keratitis were much less common in this study (6%) than in the study by MacEwen and associates[8] (22%). This decline may be attributable to improved medical treatment of herpes simplex virus recurrences.[10]

Fifteen (10%) of the regrafts were performed in eyes with keratoconus. Seven of these grafts were performed for severe astigmatism uncorrectable with selective suture removal, contact lenses, and relaxing incisions. The number of years between the first and second grafts for eyes with keratoconus was significantly higher (average, 19 years) than that for those eyes with herpes simplex virus, interstitial keratitis,

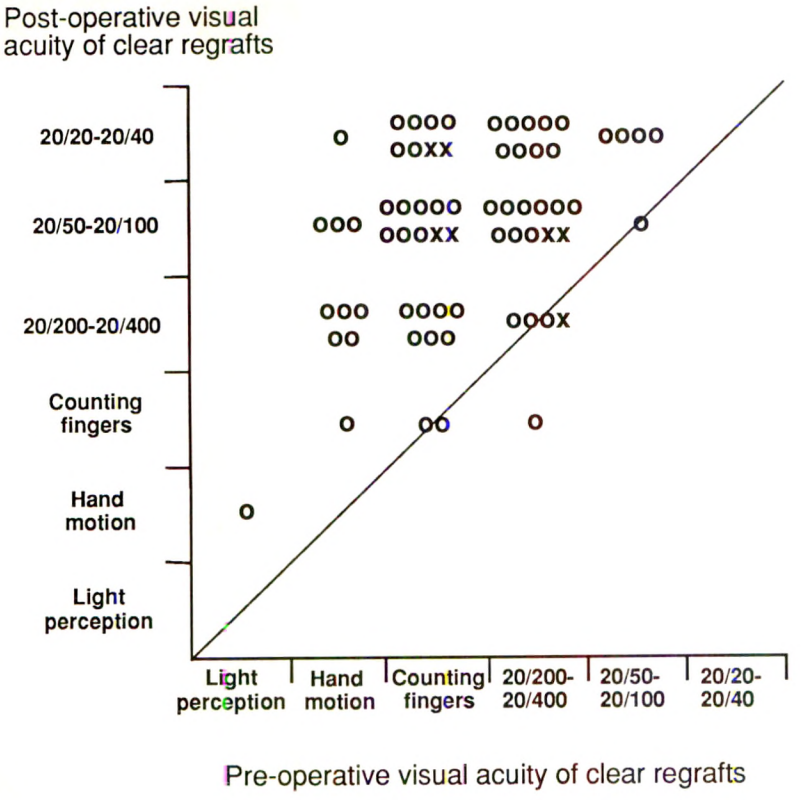

Figure (Rapuano and associates). Scattergram of preoperative and postoperative best-corrected visual acuities in eyes with clear regrafts and a minimum of two years of follow-up. o, one regraft; x, multiple regrafts.

Fuchs' dystrophy, aphakic bullous keratopathy, and pseudophakic bullous keratopathy (combined average, six years) (P = .0001). In those keratoconus regrafts performed for severe astigmatism, the average time between the grafts was even longer (23 years). In the period of the 1940s through the 1960s, the size of the transplants used in penetrating keratoplasties for keratoconus was often smaller than the transplants used today, which frequently resulted in higher amounts of astigmatism because all of the thinned cone was not removed.[11,12] The trend toward larger grafts in keratoconus patients and improved contact lens technology should reduce the number of regrafts for severe astigmatism in the future.

Pseudophakic bullous keratopathy was the leading indication for the initial corneal transplant in this series of regrafts. At the time of initial transplant, 26 of 29 intraocular lenses were left in the eye. Ten years ago, efforts were often made to retain the intraocular lens at the time of transplant.[13-16] More recently it has been suggested that the removal of most iris-supported and all closed loop anterior chamber intraocular lenses, and possibly exchanging them with a flexible anterior chamber intraocular lens or a posterior chamber intraocular lens, leads to improved prognosis for corneal transplant survival.[17-19] Over the six-year period of our study, 526 first grafts for pseudophakic bullous keratopathy were performed at our institution.[1] In approximately one half (260, 49%) of these cases, the intraocular lens was left in the eye. Yet, in this study, 26 of 29 (90%) eyes requiring a second graft for pseudophakic bullous keratopathy had had the intraocular lens left in at the time of the first graft. Although some of the eyes in this study had their first corneal transplant for pseudophakic bullous keratopathy before 1983, but given that most grafts that fail will do so within 18 to 24 months, these data suggest that removing or exchanging the intraocular lens may have had a beneficial effect on graft survival. The data from the intraocular lens management at the time of the second graft show little difference in outcome relating to the disposition of the intraocular lens, which is in contrast to what others[17,18] have shown about the management of the intraocular lens at the time of first graft. Our numbers, however, are small.

Cowden, Kaufman, and Polack[6] found that 32 of 51 (64%) of the regrafts they studied, which

had had at least one year follow-up, were clear. Of the eyes with clear grafts, they found that 85% had a visual acuity that had improved at least two lines and was better than 20/200. In another study, Robinson[7] found only 12 of 47 (26%) regrafts that had a visual acuity of 20/300 or better with a minimum of one year follow-up. He included, however, graft failures in his visual acuity data. MacEwen and associates[8] reported that 28 of 41 (68%) regrafts were clear at the end of their ten-year study. They found that if a graft survived at least two years, then the chance for continued survival was high. For all eyes in their study with a minimum of six months of follow-up, they found that 49% had a visual acuity between 20/20 and 20/200. Insler and Pechous[20] looked specifically at visual acuity results in repeat corneal grafts. They found that six of 18 eyes after one corneal graft had a visual acuity of 20/100 or better; of the 11 eyes that had undergone multiple regrafts, only one had a visual acuity of 20/100 or better. Our results, like those of MacEwen and associates,[8] show a relatively rapid rate of regraft failure over the first 18 months (22% failure rate). This rate levels out to 26% at four to six years. Our data suggest that if a regraft remains clear for the first 18 months, it has an excellent chance for survival. Although it is difficult to compare visual acuity data between these studies, it appears that visual prognosis after regraft may be improving. Multiple regrafts do not have a statistically significantly higher failure rate than first regrafts, and visual acuity data also appear comparable, even though the number of multiple regrafts is small. We believe that the graft clarity and visual acuity results are relatively good for first corneal regrafts and multiple regrafts and better than what might be expected from previous studies.

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HMB-45 Antibody Reactivity in Pigmented Lesions of the Conjunctiva

Ben J. Glasgow, M.D., Laurie C. McCall, M.D., and Robert Y. Foos, M.D.

Conjunctival pigmented lesions, including ten compound nevi, three subepithelial nevi, two acquired melanoses, and six melanomas, were examined histologically and immunohistochemically to determine the specificity of mouse monoclonal HMB-45 antibody for these lesions. Eleven of 13 nevi, two of two acquired melanoses, and six of six melanomas stained with this antibody. Conjunctival melanomas showed intense and diffuse cytoplasmic staining; compound nevi and subepithelial nevi showed less intense but diffuse reaction. There was strong staining in melanocytic cells at the junction of the epithelium and substantia propria in compound nevi and acquired melanoses. Unlike skin nevi, conjunctival nevi show HMB-45 reactivity in their stromal components. Immunoreactivity to HMB-45 does not distinguish benign from atypical or malignant melanocytic lesions of the conjunctiva.

One difficulty in the diagnosis of pigmented lesions of the conjunctiva is distinguishing atypical nevi and acquired melanoses from malignant conjunctival lesions. Lesions classified histologically as being at low risk of malignant progression have recurred as malignant lesions.[1] The use of immunohistochemical markers to identify melanocytic cells capable of proliferation is an attractive possibility for distinguishing benign and premalignant lesions from malignant lesions. Presumably, HMB-45 antibody can identify actively proliferating melanocytes, because immunoreactivity has been demonstrated in melanomas and junctional nevi of skin but not in intradermal nevi.[2]

In this study, we sought to determine the pattern of immunoreactivity of HMB-45 to pigmented lesions of the conjunctiva and to explore this antibody's potential to identify actively proliferating melanocytic cells in benign and malignant lesions. We hoped that this antibody could distinguish lesions capable of proliferation from inactive benign lesions.

Material and Methods

Blocks from ten compound nevi, three subepithelial nevi, two primary acquired melanoses, and six malignant melanomas were available from the UCLA Ophthalmic Pathology Division. The charts of these cases were reviewed to determine the clinical extent and behavior of the lesions.

Ten serial sections were recut from each block. One section was stained with hematoxylin and eosin. The other sections were used for immunohistochemical staining with HMB-45 antibody (Dako Corp., Santa Barbara, California). All hematoxylin and eosin sections were coded, reviewed, and classified by one of us (B.J.G.). The diagnoses made were compared to original diagnoses made by another one of us (R.Y.F.). In all cases, the diagnoses were consistent.

Immunohistochemical staining was performed by using the avidin-biotin peroxidase technique.[3] Mouse monoclonal antibody HMB-45 was the primary antibody, and antimouse antibody (Lipshaw, Detroit, Michigan) was the secondary antibody. Malignant melanomas of skin were used as positive controls, and sections of human spleen, lymph node, and nor-

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mal skin were used as negative controls. For each conjunctival lesion, an additional negative control with deletion of the primary antibody was performed.

Five concentrations of HMB primary antibody (1:50, 1:500, 1:1,000, 1:5,000, 1:10,000) were used initially to determine the optimal concentration for staining skin and conjunctival melanomas without background reactivity. The HMB-45 was incubated with tissue sections for four hours at all concentrations tested. All conjunctival lesions were tested with positive and negative controls at the optimal titers of HMB-45, 1:5,000. The percentage of cells that stained positively in each section was estimated by two observers independently. Discrepancies were settled by the two observers later.

Results

The age range of ten patients with benign nevi was 5 to 41 years. Six of ten patients were under 20 years of age. Clinical charts showed that most patients had had the lesions for many years. Four lesions were removed because of increasing size, and others were removed for cosmetic reasons. One lesion had been shown to remain the same size for years as documented by serial photographs. None of the lesions classified as nevi or benign acquired melanoses recurred.

The optimal concentration of HMB-45 antibody that appeared to stain melanoma cells in skin specifically was found to be a 1:5,000 dilution of the reconstituted antibody (Dako Corp.). At this concentration, there was specific staining of tumor cells without background staining. Six of six conjunctival melanomas showed diffuse and intense staining with HMB-45 antibody (Table). Most tumor cells (>90%) were stained in each case, including tumor cells within the layers of the epidermis (Figs. 1 and 2). The HMB-45 antibody stained 11 of 13 nevi. Eight of ten compound nevi and three of three subepithelial nevi showed staining with HMB-45 (Fig. 3). In most cases, the staining was less intense than with melanomas but still distinctly positive (Fig. 4). Eight of 13 nevi showed positive staining in about 50% or more of the nevus cells. In three lesions, more than 90% of the cells were reactive with HMB-45. In compound nevi, the junctional component was usually more heavily stained than the intraepithelial component.

TABLE
HMB-45 REACTIVITY IN PIGMENTED CONJUNCTIVAL LESIONS

	POSITIVE STAINING	
TYPE OF LESION	SPECIMENS	≥50% OF CELLS
Compound nevus		
Junctional	8/10	5/10
Subepithelial	5/10	3/10
Subepithelial nevus	3/3	2/3
Acquired melanosis	2/2	1/2
Malignant melanoma	6/6	6/6

Only two benign acquired melanoses were included in this study. Neither lesion could be classified as atypical. One lesion showed staining of more than 90% of cells, and the other lesion showed staining of less than 10% of cells (Fig. 5). In a few sections, occasional normal-appearing melanocytes adjacent to nevi stained weakly for HMB-45. None of the sections of spleen, lymph node, normal skin, conjunctival epithelial cells, blood cells, or nerves (negative controls) reacted with HMB-45 antibody. Sections in which primary antibody was deleted showed no peroxidase activity (negative controls).

Discussion

Melanocytic lesions of the conjunctiva have been difficult for the pathologist to diagnose. Jay[4] found the nevi misdiagnosed as melanomas in 43 of 400 pigmented lesions. Nine nevi and three acquired melanoses were originally misdiagnosed as melanomas in 126 pigmented lesions described by Liesegang and Campbell in the Mayo Clinic series.[5] Folberg and associates[6] commented on the difficulty in distinguishing junctional nevi from primary acquired melanoses with atypia.

Additionally, the histologic appearance of the earliest detectable malignant lesion is unclear. Jay[4] stated that malignancy could be designated in lesions in which pigmented cells exhibit anaplasia but are confined to the basal layer, but added that this condition is difficult

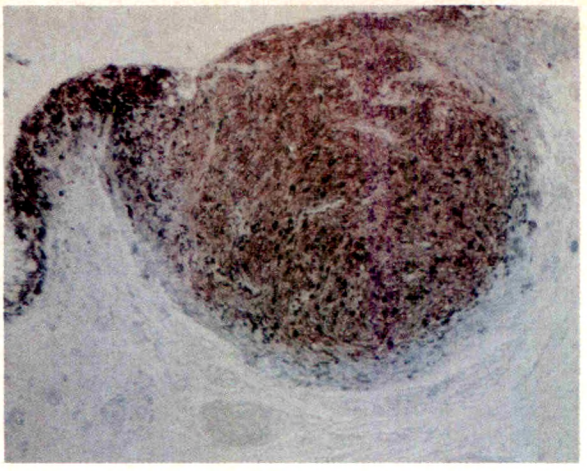

Fig. 1 (Glasgow, McCall, and Foos). Microscopic section of a conjunctival melanoma shows marked diffuse reactivity of HMB-45 antibody (× 40).

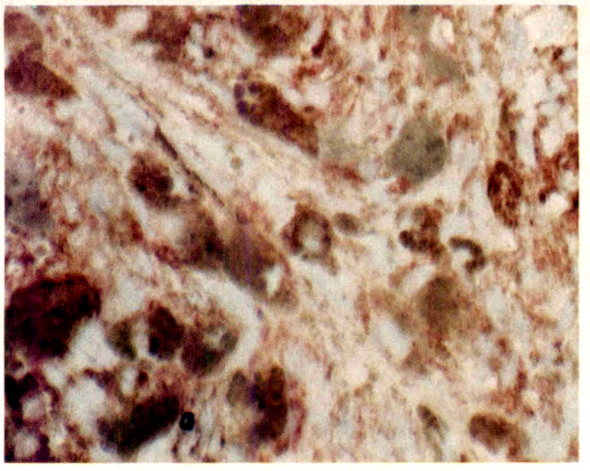

Fig. 2 (Glasgow, McCall, and Foos). Enlargement of Figure 1 shows red-brown granular staining in tumor cytoplasm. Melanin appears green (× 400).

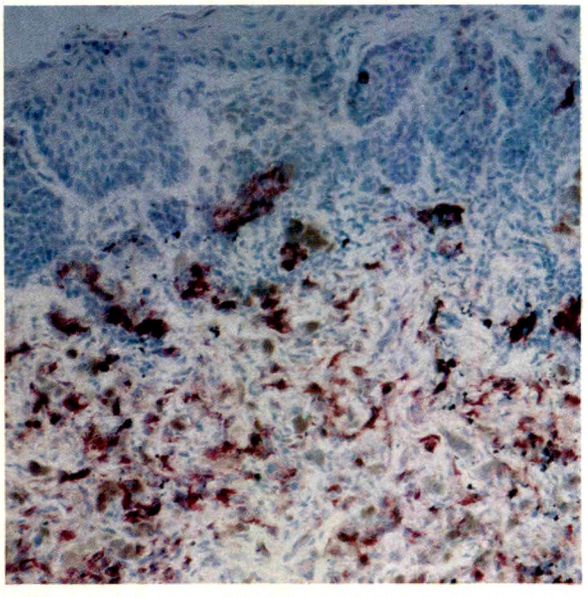

Fig. 3 (Glasgow, McCall, and Foos). Microscopic section shows red-brown reactivity of HMB-45 antibody to nevus cells in the substantia propria (× 100).

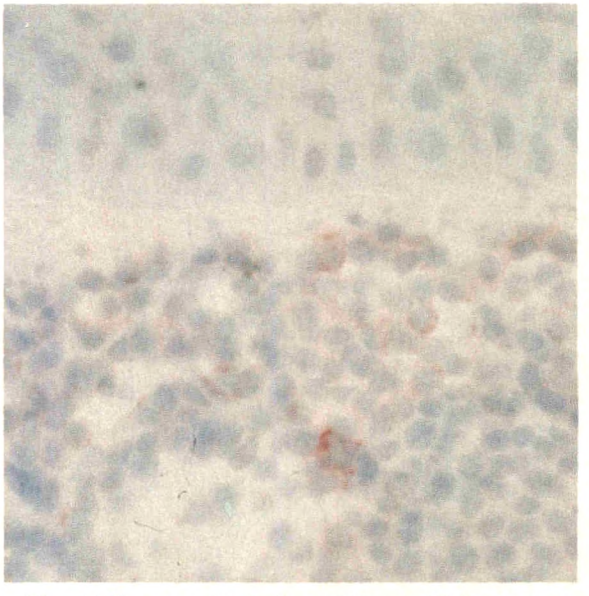

Fig. 4 (Glasgow, McCall, and Foos). HMB-45 antibody shows slight reactivity with nevus cells in the substantia propria in a section of a conjunctival subepithelial nevus (× 400).

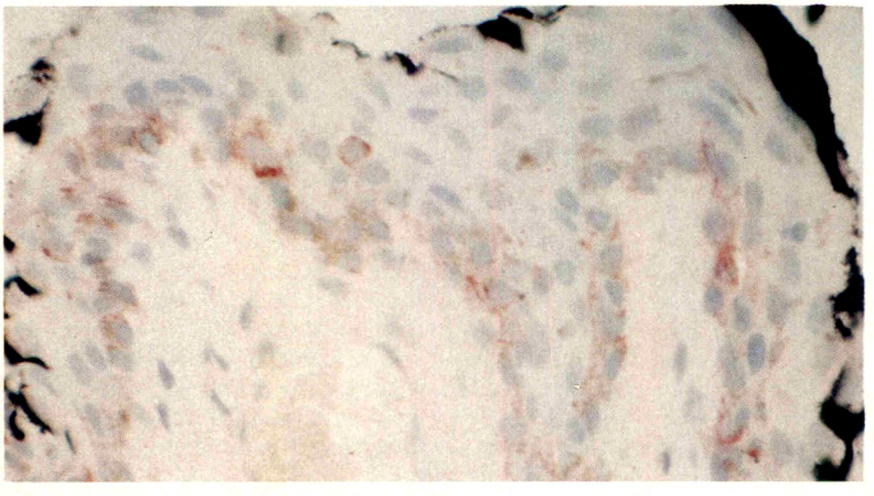

Fig. 5 (Glasgow, McCall, and Foos). Microscopic section of benign acquired melanosis shows marked reactivity in melanocytes at the basal layer of the epithelium with HMB-45 antibody. Black marking ink is evident at the margins of the specimen (× 400).

to distinguish from that of benign melanoses. The presence of an architectural pattern more advanced than basilar hyperplasia in combination with cytologic atypia has been suggested as a criterion for acquired melanoses at risk for progression to malignant melanoma.[1,7,8] Four of 18 patients designated as at low risk for progression by this criterion, however, later developed conjunctival malignant melanoma.[1] Distinguishing benign from premalignant phenotypes in these lesions cannot always be done histologically. An antibody that could identify actively proliferating cells might distinguish benign lesions from malignant or premalignant lesions.

There are several melanoma-selective antibodies, including S-100, NKI/C-3, Ortho Mel-1, Ortho Mel-2, BM 24-2, BM 34-1, and HMB-45. The S-100 antibody is known to stain a variety of tumor cells and is not specific to melanomas or cells of neural crest origin.[9,10] The NKI-3 antibody reacts with neuroendocrine tumors[11] and adenocarcinomas of breast, prostate, and ovary.[12] The S-100, NKI/C-3, Mel-1, Mel-2, BM 24-2, and BM 34-1 antibodies all react with nevocytes of skin.[13]

The HMB-45 monoclonal antibody was generated from an extract of malignant melanoma taken from an axillary lymph node by using a mouse hybridoma.[2] This antibody has been shown to be relatively specific for malignant melanoma.[14-16] It also has been reported to react, however, with cells of neuroectodermal tumor of infancy,[17] junctional nevi of skin,[2,16] Spitz nevi,[18] and neuroblastoma.[19] It does not appear to stain intradermal nevi of skin.[2] Because intradermal nevi are considered quiescent lesions, it has been hypothesized that HMB-45 recognizes epitopes expressed only in proliferating benign and malignant melanocytes.[2] Junctional nevi of skin react with this antibody presumably because the nevus cells are actively proliferating. One conjunctival nevus was reported not to stain with HMB-45.[20] Other investigators have found that junctional conjunctival nevi stain with HMB-45 (Wagner, D. G., and McDonnell, J. M., unpublished data). Our data suggest that unlike skin intradermal nevi, conjunctival subepithelial nevi contain antigens reactive with HMB-45 antibody.

The HMB-45 antibody does not appear useful in differentiating those conjunctival lesions that have the capability for intraepithelial expansion, because even benign subepithelial nevi and benign acquired melanoses stained with this antibody.

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OPHTHALMIC MINIATURE

Melville's weak eyes limited his reading to books with large type. Here is what he wrote to his editor and friend Evert Duyckinck on acquiring his first large-type edition of Shakespeare:

It is an edition in glorious great type, every letter whereof is a soldier, & the top of every "t" like a musket barrel. Dolt & ass that I am I have lived more than 29 years, & until a few days ago, never made close acquaintance with the divine William. Ah, he's full of sermons-on-the-mount, and gentle, aye, almost as Jesus . . . . I am mad to think how minute a cause has prevented me hitherto from reading Shakespeare. But until now, every copy that was come-atable to me, happened to be in a vile small print unendurable to my eyes which are tender as young sparrows . . .

Mary K. Bercaw, *Melville's Borrowings*
The Log of Mystic Seaport 41(2):35, 1989

Peribulbar Anesthesia for Strabismus Surgery

Reginald J. Sanders, M.D., Leonard B. Nelson, M.D., and James A. Deutsch, M.D.

We prospectively studied 76 patients to analyze the effectiveness of peribulbar anesthesia during strabismus surgery. The patients, ranging in age from 14 to 77 years, were given anesthesia with standard preoperative medication and a peribulbar injection of a mixture of 2% mepivacaine hydrochloride and hyaluronidase. Only one of the 76 patients required an additional injection of anesthetic to achieve adequate anesthesia. No morbidity was associated with the peribulbar anesthesia. Local anesthesia, particularly retrobulbar anesthesia, has been used as an alternative technique in an attempt to reduce the morbidity and mortality associated with general anesthesia in ocular surgery, particularly in those patients with high-risk characteristics. Even with retrobulbar anesthesia, however, there is a risk of morbidity and, in rare cases, mortality. Our results suggest that the use of peribulbar anesthesia is a safe and effective means of anesthesia in strabismus surgery because of minimal associated morbidity.

PERIBULBAR ANESTHESIA has been reported as an alternative for retrobulbar anesthesia in anterior segment surgery.[1-4] We used peribulbar injection in a wide variety of procedures to correct strabismus.

Subjects and Methods

We prospectively studied 76 consecutive patients from February 1989 to December 1989. All of the patients, who ranged in age from 14 to 77 years, underwent strabismus surgery under local anesthesia at our institution. The patients were discharged on the day of their operation. The standard preoperative medications, which included combinations of fentanyl citrate (2 mg/kg of body weight), diazepam (0.25 mg/kg of body weight), and diphenhydramine hydrochloride (1.25 mg/kg of body weight), were administered intravenously by an anesthesiologist in dosages based on age, weight, and general health. All of the patients received nasal oxygen and cardiac monitoring throughout the procedure. All of the patients were awake and alert when the peribulbar injection was given. The total peribulbar solution of 5 ml consisted of a mixture of 2% mepivacaine hydrochloride and 150 units of hyaluronidase. The injections were administered with a 25-gauge, 1.6-cm disposable needle on a 5-ml syringe. With the patient fixating in primary position, the needle was inserted through the skin at the junction of the lateral and middle thirds of the inferior orbital rim underneath the globe. Next, 3 ml of the anesthetic was slowly injected. The remaining 2 ml was injected between the superior orbital rim and the globe, using the supraorbital notch as a guide. Careful digital massage was then performed for several minutes. The pupil dilation and conjunctival chemosis were usually noted immediately after the block. Rarely, the pupil dilation was delayed five to ten minutes. After the pupil dilation, all patients were given one drop of 2.5% phenylephrine hydrochloride to topically vasoconstrict the conjunctival vessels. No facial block was given.

All of the patients underwent a variety of strabismus operations. Twenty-five of the patients had had previous ocular surgery. Some patients had medical problems that put them at risk for general anesthesia. After each operation the patients were closely monitored in the recovery room. Each patient was graded by using a criterion of two points each for alertness, motor function, color and temperature, respiration, and circulation (perfect score, 10).

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Results

Ocular movements continued for approximately ten minutes after the block. Occasionally some ocular movements occurred during the surgery even though adequate anesthesia was administered.

Only one patient required supplemental peribulbar anesthesia. After successful, comfortable recession of the right lateral rectus muscle of 16 mm, the right superior oblique muscle caused enough pain that 0.3 ml of supplemental lidocaine was injected into the superonasal quadrant. Another patient had a tuck of the right superior oblique muscle, yet had no discomfort. Of the 11 patients who had superior rectus muscle recession, seven patients described a pulling sensation during the procedure but no ocular pain. These patients remained comfortable with supplemental topical anesthesia.

There were no major ocular or systemic complications after the use of the peribulbar block. All of the patients were alert and awake during and after the procedure. All patients achieved perfect scores when examined in the recovery room for alertness, motor function, color and temperature, respiration, and circulation.

Discussion

Retrobulbar anesthesia is the most common form of local anesthesia for ocular surgery. The technique, first described by Knapp[5] in 1884 when he injected cocaine into the retrobulbar space, has undergone many modifications.[6-10] The advantages of retrobulbar anesthesia over general anesthesia include reduced mortality and morbidity, shorter duration of the anesthetic and recovery period, and lower cost, particularly in common procedures such as cataract surgery. Despite the advantages of retrobulbar anesthesia in ocular surgery, rare but significant complications have been reported, including blindness, respiratory arrest, direct injections into the central nervous system, and globe perforation.[11-26] Attempts have been made to reduce further the morbidity of retrobulbar blocks.

Injection of the local anesthetic into the periorbital space (peribulbar block) instead of directly into the muscle cone, as is done in retrobulbar anesthesia, is gaining popularity because of its similar anesthetic result and lower morbidity.[4] Theoretically, the peribulbar anesthetic diffuses into the muscle cone with direct inhibition of the neuromuscular junction of the extraocular muscles and ciliary ganglion. Because the injection is outside the muscle cone, there is no risk of coming in contact with the optic nerve, subdural and subarachnoid space, or central retinal artery, all of which are implicated in the complications of retrobulbar anesthesia.[27] Additionally, using the shorter needle should diminish the risk of entering the optic nerve or perforating the globe. An anatomic study on the path length of the retrobulbar needle showed that a retrobulbar needle could perforate the optic nerve in over 11% of the population.[28] This is particularly important when the globe is long, as in a myopic eye. A perforated globe with the use of peribulbar injection, however, has been reported.[29]

In our study, less anesthetic was needed to achieve adequate anesthesia than in many previous studies of peribulbar use for anterior segment surgery. An exception was the study by Weiss and Deichman[4] in which they described the use of 5 ml of anesthetic for the peribulbar blocks. Perhaps this is because only anesthesia and not akinesia was necessary to proceed with comfortable and safe muscle surgery, unlike cataract surgery. Therefore a smaller volume of anesthetic is sufficient for strabismus surgery.

Conjunctival chemosis and pupillary dilation may be used as early clinical signs that there is adequate anesthesia, even though pupil dilation may take longer to develop. The chemosis probably represents diffusion of the anesthetic from the periorbita. The pupillary dilation is pharmacologic paralysis of the ciliary ganglion, which is wide diffusion of the injected anesthetic.

The use of mepivacaine hydrochloride and hyaluronidase in a retrobulbar block offers three to four hours of continued anesthesia after strabismus surgery.[30] Since the same agents were used in this study, the same short duration of anesthesia can be expected. This is particularly important when adjustable sutures are used in strabismus surgery and can be modified the same day, instead of the patient returning the next day.

Most of the patients remained comfortable with a single peribulbar injection. Only one patient, who had an advancement of the superior oblique muscle, required a supplemental

injection. Seven of the 11 patients who had superior rectus muscle recession felt an unusual pulling sensation. When patients had any pulling sensation with traction on a particular muscle, only the superior muscles were involved. The nerves that supply both the superior oblique muscle and the superior rectus muscle lie outside the muscle cone. The peribulbar block may be most effective in anesthetizing those muscles within the muscle cone when the actual injection of the anesthetic agent is outside the muscle cone. When operating on the superior muscles, perhaps more anesthetic agent should be used for the superior injection.

The diverse medical problems, ages, and lengths of surgery in this study show that peribulbar anesthesia can be used effectively in many clinical settings. The use of the peribulbar injection in those patients with morbid obesity is particularly interesting. These patients have an increased incidence of cardiac disease and hypertension, which increases the risk of morbidity and mortality when using general anesthesia. Peribulbar anesthesia can potentially lower the risk of anesthesia in these patients.

The previously reported methods of local anesthesia during strabismus surgery include retrobulbar injection[30] and topical anesthesia.[31,32] Topical anesthesia, although effective, often has to be supplemented with more topical or injected anesthetics. Peribulbar injections require considerably less supplemental anesthesia and provide comfortable anesthesia for the patient. Additionally, like other forms of local anesthesia, the use of peribulbar anesthesia does not preclude assessment of a restrictive muscle disorder by forced duction testing.

Our study suggests that the peribulbar injection is an effective and safe means of anesthesia for strabismus surgery. This was not a controlled study, however, and perhaps a double-masked clinical study with a larger number of patients would be useful in the future.

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OPHTHALMIC MINIATURE

Such was the intensity of Nonna's scrutiny, in fact, that one evening in Riga she unwittingly detected in my right eye the result of cataract surgery; barely visible to the naked eye except to medical specialists, it had gone unnoticed for four years by my relatives or closest friends. "There is a tiny, tiny golden fleck on your right eye," she observed, "which makes it a *trifle* different from your left eye." She was cheered to hear that the reflection was caused by a plastic lens implant rather than by faulty makeup . . .

Francine du Plessix Gray, *Soviet Women. Walking the Tightrope*
New York, Doubleday, 1989, p. 162

Limbal-based vs Fornix-based Conjunctival Flaps in Combined Extracapsular Cataract Surgery and Glaucoma Filtering Procedure

J. Franklin Murchison, Jr., M.D., and M. Bruce Shields, M.D.

Extracapsular cataract extractions and posterior chamber intraocular lens implantations combined with glaucoma filtering procedures were done in 47 eyes of 43 consecutive patients who had coexisting cataract and glaucoma. A limbal-based conjunctival flap was used in 22 patients and a fornix-based flap was used in 25 patients; the surgical technique was otherwise identical in all patients. Patients were followed up for a minimum of six months (mean, 18 months). Long-term intraocular pressure control and visual acuity were similar in the two groups, although the limbal-based group had significantly better early postoperative intraocular pressure control. Because control of intraocular pressure during the early postoperative period is a principal benefit of combined cataract and glaucoma surgery, we prefer the limbal-based conjunctival flap.

THE SURGICAL MANAGEMENT of coexisting cataract and glaucoma basically consists of the following three options: cataract extraction alone; glaucoma filtering surgery alone followed by cataract extraction as a second procedure (two-stage approach); or glaucoma filtering procedure combined with cataract extraction (combined procedure). One approach to selecting from among these options has been described by one of us (M.B.S.),[1,2] although opinions vary among surgeons about the indications.

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Since the 1970s intracapsular cataract extraction combined with trabeculectomy has undergone several modifications in the type of fistula used and in the shift to extracapsular cataract extraction with intraocular lens implantation. Another variation in technique that has been studied is limbal-based vs fornix-based conjunctival flaps. In two reported series, no significant difference in glaucoma control was observed between the two types of conjunctival flaps,[3,4] although the limbal-based approach was associated with a higher complication rate.

One of us (M.B.S.) compared the limbal-based and fornix-based conjunctival flap in extracapsular cataract extraction and posterior chamber intraocular lens implantation combined with a glaucoma filtering procedure (guarded sclerectomy), which is a variation of the standard trabeculectomy used in combined procedures.

Patients and Methods

The consecutive patients in this study had coexisting cataract and glaucoma. Combined extracapsular cataract extraction and glaucoma filtering procedure with posterior chamber lens implantation was performed by one of us (M.B.S.) at our institution. The only variation in technique was the use of either a limbal-based or fornix-based conjunctival flap. Patients who received one technique or the other were clustered; those who received a limbal-based flap underwent surgery at the beginning or end of the study. All patients had postoperative examinations by the primary surgeon on postoperative days 1 and 2, and postoperative weeks 1 and 2. Subsequent follow-up care was continued by the primary surgeon or the referring ophthalmologist. Each patient had a minimum follow-up of six months, and no patient was

excluded from the study. This study is based on a review of the patients' hospital and clinical records. Long-term follow-up data were obtained from the referring ophthalmologist when they were not available in Duke Eye Center records.

Patients chosen for the combined procedure had cataracts that significantly affected vision and glaucoma at various levels and degrees of control. Some patients had borderline control of intraocular pressure despite the use of many medications and laser trabeculoplasty, whereas others were unable to tolerate or comply with the recommended medical therapy. In other patients, the intraocular pressure was well controlled by a low dose of well-tolerated medication, but moderate-to-advanced glaucomatous damage put the eye at risk of further irreversible visual loss, should a significant pressure increase have occurred in the early postoperative period. Finally, in some patients, the pressure was uncontrolled despite maximum medical and laser therapy. Under these circumstances, we usually prefer a two-stage approach, but the combined procedure was selected for these particular patients because there was either an urgent need to restore vision, or two procedures were not feasible. There were no specific indications for using either the limbal-based or the fornix-based conjunctival flap.

The glaucoma filtering procedure combined with cataract extraction was first described by Spaeth and Sivalingam[5] in 1976. Since then, several modifications have been described with both intracapsular and extracapsular cataract extraction.[1,2] In this series, a fornix-based or a limbal-based conjunctival flap was created superiorly.

For the fornix-based conjunctival flap, a peritomy with a 10-mm chord arc was created in the superior quadrants, that is, from approximately the 10:00 o'clock meridian to the 2:00 o'clock meridian. The conjunctiva and Tenon's capsule were dissected together from the underlying episclera for approximately 6 mm back from the corneoscleral limbus by using blunt and sharp dissection. For the limbal-based flap, an incision was made through the conjunctiva and Tenon's capsule approximately 8 mm from the corneoscleral limbus in the superior 120 degrees, and the two layers were dissected together from the underlying episclera down to the corneoscleral limbus. In all eyes, a half-thickness corneoscleral incision was made from approximately the 10:00 o'clock meridian to the 2:00 o'clock meridian. The incision began 1 mm posterior to the limbal junction, extended 2 mm back at the 12:00 o'clock meridian in a smooth curve, and completed 1 mm from the corneoscleral limbus. A lamellar dissection was then performed from the depth of the incision to the corneoscleral limbus, which created a flap of limbal tissue (Figs. 1 and 2).

If the pupil was less than 5 mm after attempted dilation, it was enlarged by creating two inferior sphincterotomies at approximately the 4:00 and 8:00 o'clock meridians and a sector iridotomy at the 12:00 o'clock meridian. In eyes with larger pupils, a peripheral iridectomy was made after creating the fistula. An anterior capsulotomy was performed with sodium hyaluronate in the anterior chamber, the lens nucleus was expressed, and the cortex was removed with an irrigation-aspiration instrument. After implantation, the posterior chamber intraocular lens was rotated until the haptics were horizontally oriented.

A fistula of approximately 2 × 3 mm was then excised from the posterior lip of the corneoscleral incision by using either a sclerectomy punch or Vannas scissors (Fig. 3). The corneoscleral incision was then approximated with two preplaced 7-0 polyglactin sutures and six 10-0 nylon sutures, which brought the anterior limbal flap as a guard over the fistula. The limbal-based conjunctival flaps were closed with a running 10-0 polyglycolic acid suture, and the fornix-based flaps were approximated with two wing sutures of the same material, which pulled the free edge of the flap over the peripheral cornea.

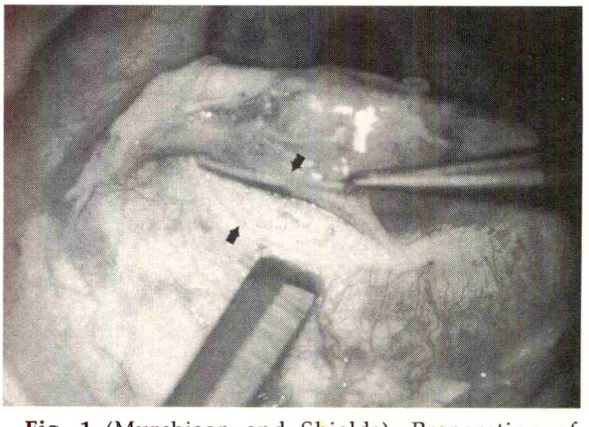

Fig. 1 (Murchison and Shields). Preparation of beveled corneoscleral incision (arrows) beneath limbal-based conjunctival flaps.

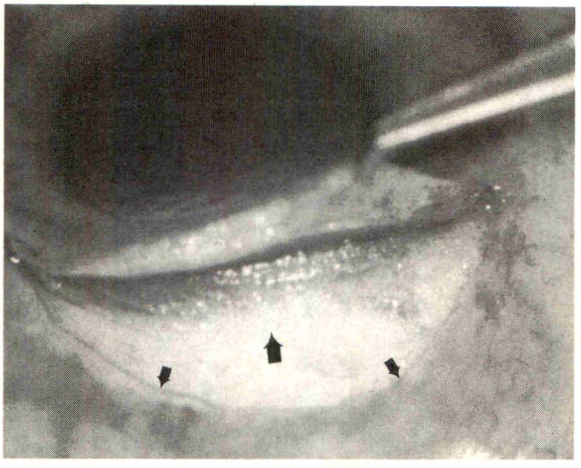

Fig. 2 (Murchison and Shields). Beveled corneoscleral incision (large arrow) with fornix-based conjunctival flap (small arrows show margin of retracted conjunctival flap).

Subconjunctival injections of dexamethasone and gentamicin were given inferiorly at the end of the procedure. Standard postoperative medications consisted of an antibiotic-corticosteroid ointment four times daily and 1% cyclopentolate solution twice daily with the antiglaucoma medications as required.

Data were analyzed statistically using Fisher's exact test and multivariate analysis of variance.

Results

The fornix-based conjunctival flap was used in 25 eyes, and the limbal-based approach was used in 22 eyes. The two groups were similar with respect to age (mean, 73 years; range, 56 to 91 years), race (35 white, eight black), gender (24 women, 19 men), type of glaucoma (39 primary open-angle, three combined mechanism, and five secondary glaucomas), degree of glaucomatous damage (33 with advanced nerve damage), glaucoma therapy (mean of 2.6 medications per patient, and laser trabeculoplasty in 19 eyes), and duration of postsurgical follow-up (minimum, six months; mean, 18 months) (Table 1).

The intraocular pressures on postoperative days 1 and 2 in the two groups were compared (Table 2). All patients in the limbal-based group had a decrease in pressure from baseline on day 1, and 21 of 22 patients had a reduction

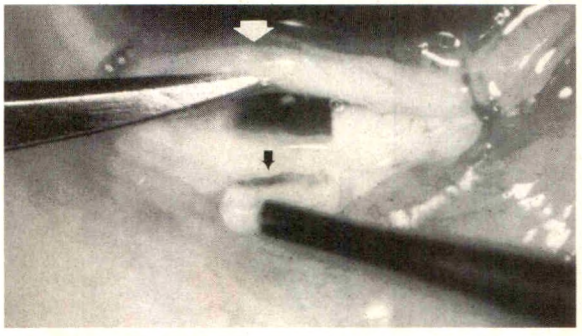

Fig. 3 (Murchison and Shields). Fistula (large arrow) beneath anterior lip of corneoscleral incision, as performed with either the limbal-based or fornix-based conjunctival flap technique (small arrow shows block of deep limbal tissue with trabecular meshwork removed from fistula site).

on day 2. In the fornix-based group, 19 of 25 patients had a decrease in pressure on day 1, and 21 had a decrease in pressure on day 2. These differences were significant for postoperative days 1 ($P = .03$) and 2 ($P = .02$). Only one patient in the limbal-based group had an intra-

TABLE 1
PREOPERATIVE DATA FOR THE TWO SURGICAL GROUPS

	CONJUNCTIVAL FLAP	
	LIMBUS-BASED	FORNIX-BASED
Age		
Mean (range)	73 (56–88)	74 (56–91)
Sex		
Male/female	14/8	12/13
Race		
White/black	17/5	22/3
Glaucoma (No. of eyes)		
Primary open-angle	19 (86%)	20 (80%)
Combined mechanism	2 (—)	1 (—)
Secondary glaucoma	1 (—)	4 (—)
Visual acuity		
>20/50	0 (—)	1 (—)
20/50–20/100	10 (45%)	9 (36%)
<20/100	12 (55%)	15 (50%)
Intraocular pressure (mm Hg)		
Mean (range)	18.0 (12–27)	18.0 (11–27)
Advanced nerve damage (No. of eyes)	14 (64%)	19 (76%)
Medications (mean No. per patient)	2.4	2.7
Laser trabeculoplasty (No. of eyes)	11 (50%)	8 (32%)

TABLE 2
EARLY POSTOPERATIVE INTRAOCULAR PRESSURE FOR THE TWO SURGICAL GROUPS

	CONJUNCTIVAL FLAP			
	LIMBUS-BASED POSTOPERATIVE DAY		FORNIX-BASED POSTOPERATIVE DAY	
INTRAOCULAR PRESSURE	1	2	1	2
> 30 mm Hg (No. of eyes)	0	1	1	2
Postoperative vs preoperative (No. of eyes)				
Increased	0 (—)	1 (4%)	6 (24%)	4 (16%)
Decreased*	22 (100%)	21 (96%)	19 (76%)	21 (84%)

*Significance of difference in percentage of eyes with decreased pressure: P = .03 for postoperative Day 1 and P = .02 for postoperative Day 2.

ocular pressure greater than 30 mm Hg on either day compared with three patients who had such pressure in the fornix-based group.

Seventeen of 22 eyes in the limbal-based group had a final visual acuity of 20/40 or better compared to 14 of 25 eyes with such visual acuity in the fornix-based group (Table 3). Nineteen of 22 eyes in the limbal-based group had improved final visual acuities from baseline compared with 19 of 25 in the fornix-based group. Neither of these differences were significant by multivariate analysis. Causes of decreased vision at final examination were attributed to advanced glaucomatous damage (six eyes), age-related macular degeneration (two eyes), diabetic maculopathy (one eye), central retinal vein occlusion (one eye), and cystoid macular edema (one eye).

The final postoperative pressures were similar in the limbal-based and fornix-based groups with means of 14.7 mm Hg and 15.3 mm Hg, respectively (P = .59). A reduction in medications was possible in 15 of 22 eyes in the limbal-based group and in 15 of 25 eyes in the fornix-based group. Four eyes in the limbal-based group and two eyes in the fornix-based group required no glaucoma medications at final examination.

The filtration blebs in the limbal-based group tended to be larger and persist longer than those in the fornix-based group (mean durations, 6.1 weeks and 4.0 weeks, respectively). One eye in the limbal-based group developed an excessively large filtering bleb, which responded to local application of cryotherapy. One case of bleb encapsulation was seen with the limbal-based approach, but the intraocular pressure was controlled by reinstitution of a topical beta-blocker.

Postoperative hyphema, which was the most frequent complication, occurred in eight and five eyes in the limbal-based and fornix-based groups, respectively (Table 4). Posterior capsu-

TABLE 3
FINAL POSTOPERATIVE STATUS FOR THE TWO SURGICAL GROUPS*

	CONJUNCTIVAL FLAP	
	LIMBUS-BASED	FORNIX-BASED
Visual acuity (No. of eyes)		
>20/50	17 (77%)	14 (56%)
20/50–20/100	2 (9%)	5 (20%)
<20/100	3 (14%)	6 (24%)
Postoperative vs preoperative visual acuity (No. of eyes)		
Improved	19 (86%)	19 (76%)
Unchanged	0 (—)	2 (8%)
Worse	3 (14%)	4 (16%)
Intraocular pressure (mm Hg)		
Mean†	14.7	15.3
Range	4–24	10–22
Mean decrease	3.2	2.7
Medications (No. of eyes)		
Reduced	15 (68%)	15 (60%)
Same	5 (22%)	9 (36%)
Increased	2 (9%)	1 (4%)
Mean follow-up (mos)	18.0	18.0
Bleb duration (wks)	6.1	4.0

*Multivariate analysis of variance of all variables indicated that the differences between the two groups were not statistically significant.

†Both groups showed a significant reduction (limbus, P = .0014; fornix, P = .0021) in final mean intraocular pressures compared to the preoperative mean intraocular pressures.

TABLE 4
POSTOPERATIVE COMPLICATIONS IN THE TWO SURGICAL GROUPS

	CONJUNCTIVAL FLAP	
	LIMBUS-BASED (NO. OF EYES) (%)	FORNIX-BASED (NO. OF EYES) (%)
Hyphema	8 (36)	5 (20)
Posterior capsular opacity requiring Nd:YAG capsulotomy	4 (18)	4 (16)
Uncontrolled intraocular pressure requiring additional treatment (Nd:YAG transscleral photocoagulation)	1 (4.5)	1 (4)
Displaced intraocular lens	3 (20)	4 (17)
Flat anterior chamber requiring pressure patching or surgical reformation	2 (9)	1 (4)
Vitreous loss	4 (18)	0 (—)
Large bleb requiring additional therapy	1 (4.5)	0 (—)
Encapsulated bleb	1 (4.5)	0 (—)
Retinal detachment	1 (5)	0 (—)
Induced astigmatism [mean D]	[0.5]	[1.1]

*Fisher's exact test of all variables indicated the differences between the two groups were not statistically significant except for vitreous loss (P = .03).

lar opacification that required Nd:YAG posterior capsulotomy was the next most frequent complication, occurring in four eyes of each group. Eccentricity of the posterior chamber intraocular lens was seen in three eyes in the limbal-based group and four eyes in the fornix-based group (P = 1.0). No eye required repositioning or removal of the intraocular lens. In the limbal-based group, posterior capsular rupture with vitreous loss occurred in four eyes, all of which were in the initial cluster of patients. A rhegmatogenous retinal detachment was seen in one eye in the limbal-based group three years after the combined surgery. Two eyes in the limbal-based group and one eye in the fornix-based group had a flat anterior chamber that required either pressure patching or surgical reformation. Only one eye in each group required additional therapy (Nd:YAG transscleral cyclophotocoagulation) for uncontrolled intraocular pressure. The eye that required additional therapy in the limbal-based group had blunt trauma after the initial surgery. The glaucoma of all other eyes remained medically controlled at the last examination.

Discussion

Of the 47 eyes studied, both the limbal-based and fornix-based groups had significant improvement of both intraocular pressure (limbus, P = .0014; fornix, P = .0021) and visual acuity (limbus, P = .0005; fornix, P = .0001) compared to the preoperative status. Most eyes in both groups attained visual acuities of 20/40 or better. The major reasons for worse visual acuities were advanced glaucomatous damage and age-related macular degeneration. Our final visual acuity results were not as good as those of Jay[6] and Percival,[7] who reported that 100% and 91% of their patients, respectively, attained 20/40 or better visual acuity postoperatively with a fornix-based conjunctival flap. Our findings are similar, however, to those of Simmons and associates,[4] who noted that 60% of their patients had visual acuities of 20/40 or better at one year, and McCartney and associates,[3] who reported that 78% of their patients had final visual acuities of 20/40 or better. In the latter two studies, both limbal-based and fornix-based conjunctival flaps were used, although no direct comparison of the two groups for visual acuity was reported.

Long-term intraocular pressure control was similar between the limbal-based and fornix-based groups, with mean preoperative intraocular pressures of 18 mm Hg in both groups and final mean pressures of 14.7 mm Hg and 15.3 mm Hg (P = .59), respectively. This finding is consistent with that of Simmons and associates[4] (mean baseline pressure, 19.3 mm Hg; mean 12-month postoperative pressure, 16.3 mm Hg), and McCartney and associates[3] (mean baseline pressure, 23 mm Hg; mean final pres-

sure, 17.1 mm Hg). The glaucoma in 41 patients (96%) was controlled medically without additional surgical intervention; 18 (82%) and 19 (76%) eyes in the limbal-based and fornix-based groups, respectively, attained a final intraocular pressure of 17 mm Hg or less.

A reduction in glaucoma medications was achieved in most patients in the limbal-based and fornix-based groups (15 [68%] and 15 [60%], respectively). Only four patients (8.5%) required an increase in medications, and four eyes (18%) in the limbal-based and two eyes (8%) in the fornix-based group required no medications. In one series, there was an 85% reduction in medications, with 50% of eyes requiring no medications,[4] whereas in another series 57% of eyes required no medications postoperatively.[3] We did not believe that the use of a posterior chamber intraocular lens had a detrimental effect on glaucoma management or visual acuity, which is consistent with the findings of Neumann, Zalish, and Oliver.[8]

Transient postoperative pressure increase after extracapsular cataract extraction and posterior chamber intraocular lens implantation has been well documented. In a large series by Kooner, Dulaney, and Zimmerman,[9] 29% of eyes had a rise of 8 mm Hg or more from baseline or an absolute value greater than 23 mm Hg on the first postoperative day. This occurrence is more prevalent in eyes with preexisting glaucoma. McGuigan and associates[10] found that 62% of glaucomatous eyes had early pressure increases of greater than 7 mm Hg over baseline compared to 10% of nonglaucomatous eyes. Savage and associates[11] reported that 23% of glaucomatous eyes that were medically controlled preoperatively and 39% that were controlled with laser trabeculoplasty had pressure rises greater than 15 mm Hg over baseline in the early postoperative period. We previously reported that 29% of glaucomatous eyes had pressure increases greater than 30 mm Hg on the first two postoperative days after extracapsular cataract extraction with posterior chamber lens implantation.[12]

Several studies have shown the combination of extracapsular cataract extraction with trabeculectomy to be effective in minimizing the risk of early pressure increases compared to extracapsular cataract extraction alone,[3,12] although Percival[7] and Simmons and associates[4] noted that 21% and 29% of their patients, respectively, had early pressure increases greater than 30 mm Hg after combined surgery. In our series, four eyes (8.5%) had pressure increases greater than 30 mm Hg during the first two postoperative days. Only one patient in the limbal-based group had a pressure increase greater than 30 mm Hg compared to three patients with such pressures in the fornix-based group. All patients in the limbal-based group had reduced pressure from baseline on the first postoperative day with 21 eyes (96%) showing a pressure reduction on the second postoperative day. This finding contrasts significantly with a pressure reduction in 19 (76%) and 21 (83%) eyes on postoperative days 1 and 2, respectively, in the fornix-based group.

Only five (23%) and six (24%) filtering blebs in the limbal-based and fornix-based groups, respectively, were present at two months postoperatively. Simmons and associates[4] reported 41% of their blebs were present at two months using both types of conjunctival flaps. Although the limbal-based approach was associated with larger blebs and a slightly longer bleb survival, compared to the fornix-based group in our series (6.1 weeks vs 4.0 weeks, respectively), these differences were not statistically significant. These results may be related to aqueous leakage at the corneoscleral limbus with the fornix-based flap, which has been observed after a trabeculectomy in the early postoperative period[13,14] and may result in a smaller filtering bleb.

Postoperative hyphema occurred in 13 eyes (28%) without a significant difference between the two groups. This is similar to the finding of Jay,[6] who used a fornix-based approach and had 29% of patients with hyphemas. Simmons and associates[4] reported a hyphema rate of 45%, with 71% of hyphemas occurring in the limbal-based group and 30% occurring in the fornix-based group. All hyphemas in our series resolved without significant sequelae. There were more posterior capsular ruptures with vitreous loss in the limbal-based than in the fornix-based group (four vs zero, respectively). All ruptures, however, occurred in the initial cluster of limbal-based procedures with none in the second cluster at the end of the study, which suggests that the surgeon's learning curve with extracapsular cataract surgical techniques may have been a factor. The rate of posterior capsular opacification requiring capsulotomy was 17% (eight eyes), which is consistent with previous reports.[3,4] The small amount of induced cylinder for each of our groups (means, 0.5 diopter and 1.1 diopters in the limbal-based and fornix-based groups, respectively), is probably attributable to the posterior placement of

the corneoscleral incision. Simmons and associates[4] reported 1.96 diopters and 2.15 diopters of induced cylinder for the limbal-based and fornix-based groups, respectively.

The combination of extracapsular cataract extraction and posterior chamber intraocular lens implantation with a guarded fistula appears to be a safe and effective means of visual rehabilitation and maintenance or improvement of intraocular pressure control in eyes with coexisting cataract and glaucoma when using the described patient selection criteria. The limbal-based and fornix-based conjunctival flap techniques appear comparable with respect to visual acuity and long-term glaucoma control, although the technically more difficult limbal-based approach appears to have the advantage of better early postoperative pressure control.

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OPHTHALMIC MINIATURE

In their pottery and sculpture, the Mayan craftsmen liked to exaggerate noses, because a large nose, like an elongated head, was a sign of strength and beauty. The Maya also thought that cross-eyes made a person look very handsome. So a mother always dangled a bead from her baby's forehead. As the infant tried to focus its eyes on the bead, the eyes crossed.

Sonia Bleeker, *The Maya Indians of Central America*
New York, William Morrow and Company, 1961, p. 61

Evaluation of the Tono-Pen and the Pulsair Tonometers

Thomas A. Armstrong, M.D.

A clinical evaluation of two new portable tonometers, the Oculab Tono-Pen and the Keeler Pulsair, was performed to determine their accuracy and efficacy. Measurements were obtained in 229 eyes of 130 normal patients and compared to measurements obtained with the Goldmann applanation tonometer. The average absolute deviation for the Tono-Pen and the Pulsair was a significant 2.70 mm Hg and 2.49 mm Hg, respectively. Thirteen of 188 (7%) Tono-Pen readings and 19 of 229 (8%) Pulsair readings differed from the Goldmann readings by more than 5 mm Hg. Both instruments were highly sensitive and specific for detecting intraocular pressures greater than 21 mm Hg.

DESPITE the wide acceptance of the Goldmann applanation tonometer, it suffers from lack of portability, positional difficulties for some patients, and is difficult to master. Additionally, the transfer of ocular or systemic disease among patients is possible.

In the past several years, the Oculab Tono-Pen and Keeler Pulsair instruments have been introduced. Both of these devices are relatively portable, can be used regardless of the patient's body type or position, and are easily mastered. The results obtained are objective and not dependent on the operator's expertise. The Pulsair has the additional advantage of being a noncontact device, thus decreasing the possible spread of disease through body fluids. The disposable latex tip on the Tono-Pen should also make this instrument safe.

I compared the Oculab Tono-Pen and Keeler Pulsair instruments with the Goldmann applanation tonometer for accuracy, ease of use, and possible clinical applications. Several recent studies described the relative accuracy of the Tono-Pen[1-5] and Pulsair.[6]

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Material and Methods

The Tono-Pen is a small, hand-held, self-contained 56-g instrument based on the principle of the Mackay-Marg tonometer.[7,8] The Tono-Pen uses a 1.02-mm diameter central plunger surrounded by a larger, round foot plate. When the instrument tip is pressed against the cornea, a strain gauge senses the force generated by the plunger. As the surrounding foot plate contacts the corneal surface, the force curve levels off and a waveform is generated. A single microprocessor chip instantaneously analyzes this waveform and emits an audible click when a reading is accepted. The operator repeats these small gentle pecking movements against the anesthetized cornea until four to ten readings are accepted and averaged. The instrument emits an audible beep and provides the final reading along with the percent variability between the highest and lowest readings, which is between 5% and 20%. During the readings, the tip of the Tono-Pen is covered with a disposable latex cover, which was changed between patients in this study.

The Keeler Pulsair is a new noncontact tonometer designed with a hand piece on a 2-m cord; the hand piece can be taken directly to the patient's eye. The unit weighs 22 lbs. The hand piece is held approximately 2 cm from the patient's cornea; final adjustment is achieved by looking through the hand piece and focusing the test object on the patient's cornea. The instrument contains photodetectors that detect proper alignment and automatically deliver a ramped air impulse to the cornea. Measurement of corneal flattening is determined through a series of lenses that form an image on the photodetectors. The intraocular pressure is gauged relative to the air pressure required to produce corneal flattening; the result is a digital

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readout on the hand piece. Each triggered air impulse results in a reading. In this study, four readings were taken and recorded on each eye, as recommended by the manufacturer.

Of 130 patients chosen at random from a normal patient population, the intraocular pressures of 229 eyes were measured with the Goldmann, Tono-Pen, and Pulsair tonometers. The particular instruments used were normal commercial products; the suppliers were not aware of this investigation. All Goldmann tonometer readings were obtained on the same calibrated tonometer; care was taken to obtain an average systolic-diastolic measurement. For each patient, two readings were obtained, and the average to the nearest integer was taken if the measurements were within 2 mm Hg; otherwise three readings were averaged.

The Tono-Pen and Pulsair measurements were obtained by trained technicians after several hours of supervised practice with each instrument. The Tono-Pen was calibrated and cleaned daily in accordance with the manufacturer's instructions. All Tono-Pen measurements were repeated until a 5% variability readout was obtained. The results were recorded in a masked fashion so that the physician and technician were not aware of each other's results. The order of testing with each patient was randomized; all testing was completed within a ten-minute period.

The data were separated into three groups (4 to 15 mm Hg, 16 to 27 mm Hg, and ≥28 mm Hg) depending on the Goldmann applanation results. The mean difference and standard deviation between either the Pulsair or Tono-Pen results and the Goldmann results were calculated for each group. Because high and low readings would be equally inaccurate but would tend to produce a mean difference close to zero, the absolute values of the differences were also analyzed. Any reading above or below the Goldmann result was considered a positive error, and the mean was calculated (absolute deviation). Statistical significance was determined by using Student's *t*-test for paired data.

Many of the Pulsair readings on an individual eye showed high variability. The data were adjusted in these cases to see if the exclusion of certain data points could improve the overall accuracy of the instrument. First, the average of the four readings on each eye was calculated. Any values that differed by more than 5 mm Hg from this average were excluded, and a new average was taken with the remaining values. Both the original and the modified averages were compared with the Goldmann readings as described.

The sensitivity (false-positives) and specificity (false-negatives) were evaluated for each instrument. An intraocular pressure above 21 mm Hg was the target level that I desired to detect.

Results

The results of the comparison of the Tono-Pen and the Goldmann tonometer are shown in Table 1. The measurements obtained with these instruments were significantly different in all groups (that is, low, normal, and high intraocular pressure groups). The Tono-Pen tended to overestimate low and normal intraocular pressures. The mean difference between these instruments was only .82 mm Hg in the 18 to 27 mm Hg group. The standard deviation, however, was 3.0, indicating significant variability in the readings. Overall, the Tono-Pen readings were a mean 1.54 mm Hg higher than the Goldmann results, with a standard deviation ± 2.91 mm Hg.

The absolute values of the differences between the Tono-Pen and Goldmann readings were evaluated (Table 2). Because falsely high and low readings tend to cancel each other out, this absolute deviation is a better measure of the Tono-Pen's accuracy. The overall mean absolute deviation was 2.70 mm Hg; that is, each Tono-Pen measurement differed (higher or lower) from the corresponding Goldmann measurement by a mean 2.70 mm Hg. This mean absolute deviation was fairly consistent throughout the entire intraocular pressure range and was statistically significant in all three pressure

TABLE 1
COMPARISON OF TONO-PEN AND GOLDMANN MEASUREMENTS

GOLDMANN PRESSURE (MM HG)	NO. OF EYES	MEAN DIFFERENCE*	S.D.	P†
4–15	107	2.22	±2.60	.001
16–27	76	0.82	±3.00	.001
28–50	5	−2.20	±2.95	N.S.
Total	188	1.54	±2.91	.001

*Tono-Pen minus Goldmann.

†Student's *t*-test. N.S. indicates not significant.

TABLE 2
ABSOLUTE DIFFERENCE BETWEEN TONO-PEN AND GOLDMANN MEASUREMENTS

GOLDMANN PRESSURE (MM HG)	NO. OF EYES	MEAN ABSOLUTE DIFFERENCE	S.D.	P
4–15	107	2.88	±1.24	.001
16–27	76	2.45	±1.90	.001
28–50	5	3.00	±1.87	.02
Total	188	2.70	±1.88	.001

groups. This result explains the fairly high standard deviation seen with the mean difference calculations.

Fifty-seven of 188 (30%) of the Tono-Pen readings differed from the Goldmann readings by more than 3 mm Hg. Thirteen of 188 (7%) of the Tono-Pen results differed from the Goldmann results by more than 5 mm Hg.

The Tono-Pen was also evaluated for its ability to detect intraocular pressures greater than 21 mm Hg. Seventeen of 188 (9%) of the eyes tested with the Tono-Pen had pressures greater than 21 mm Hg when the Goldmann pressure was 21 mm Hg or less, that is, the Tono-Pen had a false-positive rate of 9%. The false-negative rate for detecting pressures above 21 mm Hg with the Tono-Pen was 5% (nine of 188 eyes). Thus, the Tono-Pen was 91% sensitive and 95% specific for detecting intraocular pressures above 21 mm Hg.

The average differences between the Pulsair and the Goldmann tonometers are shown in Table 3. The Pulsair had only a slight tendency to overestimate the low intraocular pressures but did tend to underestimate the high intraocular pressures. Moreover, the high readings served to cancel the low readings; the mean difference between the Pulsair and Goldmann intraocular pressures was only 0.56 mm Hg in the low pressure group and −0.54 mm Hg in the 16 to 27 mm Hg group. For the 229 eyes studied, the mean difference between the Pulsair and the Goldmann was 0.01 ± 3.16 mm Hg. Although this standard deviation disclosed variability in the readings, the small mean difference was not statistically significant.

Of greater importance was the absolute value of the deviation between the Pulsair readings and the Goldmann readings (Table 4). The mean absolute deviation was statistically significant in all pressure groups; it measured 2.14 mm Hg in the 4 to 15 mm Hg group, 2.84 mm Hg in the 16 to 27 mm Hg group, and 4.25 mm Hg in the greater than or equal to 28 mm Hg group. The overall mean absolute deviation for the Pulsair instrument was 2.49 ± 1.87 mm Hg.

TABLE 3
COMPARISON OF PULSAIR AND GOLDMANN MEASUREMENTS

GOLDMANN PRESSURE (MM HG)	NO. OF EYES	MEAN DIFFERENCE*	S.D.	P†
4–15	130	0.56	±2.80	.05
16–27	91	−0.54	±3.29	.001
28–50	8	−3.25	±3.31	.05
Total	229	0.01	±3.12	N.S.

*Pulsair minus Goldmann.

†Student's *t*-test. N.S. indicates not significant.

The Pulsair manufacturer recommends that the average of four readings in each eye be determined. In 74 of 229 eyes (32%), the difference between the high reading and the low reading was 10 mm Hg or more. In an attempt to improve accuracy of the instrument, any data points that differed from the mean of the four readings by greater than 5 mm Hg were excluded and a new mean measurement was calculated. The mean deviation and mean absolute deviation for this new reading were evaluated. The new adjusted mean absolute deviation, 2.57 mm Hg, was actually slightly greater than the 2.49 mm Hg mean calculated from the original data. Thus, the exclusion of seemingly false results obtained by the Pulsair did not serve to improve the instrument's accuracy.

Seventy-three of 229 (32%) Pulsair results differed from those of the Tono-Pen by more than 3 mm Hg, and 19 of 229 (8%) differed by more than 5 mm Hg. The Pulsair was found to

TABLE 4
ABSOLUTE DIFFERENCE BETWEEN PULSAIR AND GOLDMANN MEASUREMENTS

GOLDMANN PRESSURE (MM HG)	NO. OF EYES	MEAN ABSOLUTE DIFFERENCE	S.D.	P
4–15	130	2.14	±1.89	.001
16–27	91	2.84	±1.72	.001
28–50	8	4.25	±1.53	.001
Total	229	2.49	±1.87	.001

be 93% sensitive (false-positives, 17 of 229) and 94% specific (false-negatives, 13 of 229) for determining intraocular pressures greater than 21 mm Hg.

Discussion

The Oculab Tono-Pen and the Keeler Pulsair offer simplicity of use and objectivity. Our technicians were able to master the use of both instruments after brief instruction and one or two hours of practice. The end points for both instruments are digital readings rather than a subjective estimation of two moving semicircles as with the Goldmann tonometer. The measurements can be taken quickly without the need for the patient to get situated properly at the slit lamp.

Generally, the technicians preferred the Tono-Pen and almost always obtained a reliable reading (< 5% variability) on their first attempt. The Pulsair was somewhat more difficult to use; the technicians were occasionally not able to obtain four readings. Although measurement time was longer with the Pulsair, both instruments required only several minutes per patient.

The patients preferred the Tono-Pen; the instrument is small, silent, quick, and nonthreatening. Because the Pulsair is considerably quieter, simpler to operate, and allows the patient to maintain a comfortable position, it is not nearly so objectionable or startling to patients as earlier noncontact tonometers. Additionally, most patients had the benefit of topical anesthetics, which made the testing more tolerable.

A significant advantage of the Keeler Pulsair is its noncontact operation. However, Britt, Clifton, and Mills, using high-speed photography, showed microaerosol formation of the tear film during measurement with both the American Optical airpuff tonometer[9] and the Pulsair (personal communication, February 1990). Both instruments administer an approximately equal air pulse to the eye (manufacturers' data), and droplet formation was found to be present with each. Although the spread of infection, especially adenovirus, would be unlikely between patients, the examiner could be at risk, unless protective eyewear was worn. Infectious agents, however, can also be spread when removing the latex cover from the Tono-Pen or when performing Goldmann applanation.

Both the Tono-Pen and Pulsair are portable but to different degrees. The Pulsair, at 22 lbs., is best used in a clinic or office. The Tono-Pen is easily carried, which renders it suitable for bedside examinations and use in nursing homes. The Tono-Pen does, however, require batteries and a constant supply of latex covers.

However convenient, each instrument is only as useful as its results are accurate. The Tono-Pen has been evaluated in published reports; two groups of investigators[4,5] studied the Tono-Pen in cadaver eyes with manometer-controlled pressures and found a correlation coefficient of 0.99 between measurements.

Most clinical studies, however, have found a statistically significant difference between the Tono-Pen and Goldmann instruments.[1-3] Recently, Farrar and associates[10] found that the Tono-Pen was not accurate enough to obtain reliable diurnal curves.

The results of the present study confirm the results of these latter studies.[1-3,10] The average absolute deviation between the Tono-Pen and Goldmann readings was 2.70 ± 1.88 mm Hg. Thirteen of 188 (7%) of the Tono-Pen readings differed by 5 mm Hg or more. Such variability cannot be tolerated in the diagnosis or treatment of a vision-threatening disease when more accurate techniques are readily available.

The Keeler Pulsair is a recently introduced noncontact tonometer and has the advantages of a portable hand piece and patient acceptance over earlier models. The operating principle, however, has not changed. Shields[11] reviewed noncontact tonometers in 1980. His study and other studies[12,13] disclosed a fairly high coefficient of correlation between the noncontact tonometers and the Goldmann instrument. Shields[11] also found increased discrepancy in the higher pressure ranges. He concluded that the noncontact tonometer could be of use in large screening clinics.

My data show the Pulsair instrument to be reasonably accurate. The mean absolute deviation between the Pulsair and Goldmann was a significant 2.49 mm Hg. The mean absolute deviation for pressures between 16 and 27 mm Hg was 2.84 mm Hg, vs 4.25 mm Hg for pressures 28 mm Hg and higher. Because the high readings cancel out the low readings, the mean deviation between the Pulsair and Goldmann was a nonsignificant 0.01 ± 3.12 mm Hg. This seems to indicate that if enough readings were taken with the Pulsair, an accurate result could be obtained. Multiple readings, of course, would be impractical. Nineteen of 229 (8%) Pulsair readings differed from the Goldmann

readings by more than 5 mm Hg. One disconcerting feature of the Pulsair instrument was the wide range of readings obtained on the same eye. Seventy-four of 229 (32%) of the eyes tested showed a difference of 10 mm Hg or more between the highest reading and the lowest reading. Recalculation of the results after the elimination of seemingly false data points, however, did not increase the accuracy of the Pulsair. The inclination to discard apparently aberrant readings must be resisted; all data points should be included in the average.

The Tono-Pen and Pulsair are reasonably and comparably accurate instruments and are ideally suited for intraocular pressure screening by nonphysician personnel. The sensitivity and specificity for detecting pressures above 21 mm Hg were over 90% for both instruments. An average error of less than 3 mm Hg for both instruments is tolerable in a screening situation. The instruments could also be useful in an ophthalmology practice for the detection of increased intraocular pressures after laser or surgical procedures and in situations where the Goldmann tonometer cannot be used. The portability and ease of use of the Tono-Pen make this instrument ideal for bedridden patients in hospitals or nursing homes.

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Primate Trabeculectomies With 5-Fluorouracil Collagen Implants

Ben Hasty, M.D., Dale K. Heuer, M.D., and Don S. Minckler, M.D.

Bilateral trabeculectomies were performed on four normal cynomolgus monkeys. Highly purified bovine skin collagen implants with either 1 mg of 5-fluorouracil or physiologic saline (one each per monkey by randomized, masked assignment) were sutured under the scleral flaps. The randomization code was not broken until all clinical and histopathologic observations had been completed. Six weeks postoperatively, the 5-fluorouracil-treated eyes had more deeply open internal trabeculectomy ostia than the control eyes; however, the intraocular pressures were indistinguishable, the filtering blebs were only minimally different, and half of each group had trace or mild anterior subcapsular lenticular changes. Histologically, a multinucleated foreign body giant cell reaction was evident in all of the collagen implants, but the 5-fluorouracil-treated eyes had less vigorous or delayed reactions compared to the control eyes. The collagen implant appears to be a poor drug delivery system in this model of glaucoma filtering surgery, because it incites a granulomatous inflammatory reaction.

POSTOPERATIVE SUBCONJUNCTIVAL 5-fluorouracil decreases the failure rate of trabeculectomies in patients with poor surgical prognoses; subconjunctival 5-fluorouracil administration, however, is relatively impractical and is frequently complicated by corneal epithelial defects and conjunctival wound leaks.[1] An implantable, sustained-delivery system would be more practical and should improve the therapeutic index by maximizing the concentration of 5-fluorouracil in the filtering bleb while reducing the concentration of 5-fluorouracil in other ocular tissues. One such sustained-delivery device, a collagen implant manufactured from highly purified bovine skin collagen cross-linked with hexamethylene diisocyanate, extends the half-life of subconjunctival bleomycin to 275 minutes compared to 88 minutes by subconjunctival injection alone.[2] A model of filtering surgery in rabbits[3] and preliminary clinical application[4] suggest that those collagen implants may be a useful sustained-delivery system for 5-fluorouracil as well; consequently, we undertook a randomized, masked comparison of collagen implants impregnated with 5-fluorouracil and placebo collagen implants in trabeculectomies on normal cynomolgus monkeys.

Material and Methods

The study protocol was approved by the University of Southern California Institutional Animal Care and Use Committee (protocol 4281). Trabeculectomies were performed bilaterally on four nonglaucomatous cynomolgus monkeys with the following technique: The monkeys were anesthetized with ketamine hydrochloride and xylazine, after which they were intubated. Lateral canthotomies were performed; 6-0 polyglactin traction sutures were placed in the peripheral corneas. Limbal-based conjunctival flaps were dissected in the superotemporal quadrants, and the conjunctival–Tenon's capsule incisions were placed as far from the corneoscleral limbus as technically possible (approximately 10 mm). Tenonectomies were not performed. Lamellar scleral flaps (4 × 4 mm^2, measured with calipers) were dissected forward into the peripheral corneas.

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Paracentesis tracts were made temporally at the corneoscleral limbus. The internal blocks, which measured approximately 1 × 2 mm, were removed with a blade and scissors. A sector iridectomy was performed.

By randomized, masked assignment, each monkey received a sterile (gamma-irradiated), 3 × 3-mm collagen implant in one eye and a similar 3 × 3-mm collagen implant that had been impregnated with 1 mg of 5-fluorouracil in the fellow eye. The collagen implants were placed in the bed of the scleral flaps after the anterior chambers had been deepened through the paracentesis tracts with sodium hyaluronate to replace virtually all of the aqueous humor that might contact the collagen implants during surgical closures of the scleral flaps and the conjunctival wounds. Interrupted 10-0 nylon sutures were passed through the posterior corners of the scleral flaps, incorporating the posterior corners of the collagen implants to ensure that the implants would neither protrude from under the scleral flap nor migrate postoperatively.

The conjunctival–Tenon's capsule incisions were closed in two separate layers with running 8-0 polyglactin sutures on taper-point needles. Balanced salt solution was injected through the paracentesis tracts to deepen the anterior chambers and confirm watertight wound closures. Subconjunctival injections of 10 mg of triamcinolone acetonide were administered inferonasally, and atropine ointment was applied topically. The lateral canthotomies were repaired with interrupted 6-0 polyglactin sutures.

The monkeys were extubated after they were sufficiently awake to protect their airways; they were returned to their cages only after they were fully alert. Thereafter, they were carefully monitored to ensure comfort and ease in feeding and drinking.

One, two, three, four, and six weeks postoperatively, the monkeys underwent intraocular pressure measurement with a Tono-Pen and anterior segment examination (including gonioscopy four and six weeks postoperatively) with an operating microscope under ketamine sedation.

After the examination six weeks postoperatively, 0.05 ml of aqueous was aspirated through the corneoscleral limbus with 30-gauge needles, after which 0.05 ml of India ink was injected into each anterior chamber. Approximately 30 minutes later, the monkeys were killed with intracardiac sodium pentobarbital. Bilateral exenterations were performed immediately after death, and the specimens were fixed in 10% formalin for histopathologic study.

All clinical observations and histologic examinations were performed by investigators who were masked to which eyes had 5-fluorouracil collagen implants and which eyes had control collagen implants.

Results

One week postoperatively, two of the 5-fluorouracil–treated eyes had intraocular pressures of 0 mm Hg, whereas the intraocular pressures of the other two 5-fluorouracil–treated eyes and the four control eyes ranged from 4 to 6 mm Hg; throughout the remainder of the follow-up period, there were no clinically important differences in the intraocular pressures between the 5-fluorouracil–treated eyes and the control eyes (Table 1).

Six weeks postoperatively, two of the 5-fluorouracil–treated eyes had moderate-sized filtering blebs, and one of the control eyes had a small filtering bleb (the other two 5-fluorouracil–treated eyes and the other three control eyes did not have clinically evident filtering blebs). There was a distinct difference between the gonioscopic appearance of the eyes in the groups: the internal trabeculectomy ostium was deeply open in three of the 5-fluorouracil–treated eyes (in the remaining 5-fluorouracil–treated eye, the internal trabeculectomy ostium was somewhat posteriorly located, and had

TABLE 1
INTRAOCULAR PRESSURE DATA

	5-FLUOROURACIL–TREATED EYES (MM HG)			CONTROL EYES (MM HG)		
	RANGE	MEAN	S.D.	RANGE	MEAN	S.D.
Preoperatively	9–11	10.25	0.96	8–11	9.25	1.26
1 wk	0–6	2.50	3.00	4–6	5.25	0.96
2 wks	7–14	9.75	3.40	7–13	10.00	2.94
3 wks	9–16	11.50	3.32	4–13	8.75	4.92
4 wks	9–12	10.50	1.29	9–12	10.00	1.41
6 wks*	7–10	8.67	1.53	8–9	8.67	0.58

*Intraocular pressure was inadvertently not recorded on one monkey.

been occluded by peripheral anterior synechiae continuous with the ciliary body), whereas the trabeculectomy site appeared to have been filled in with fibrous tissue (two eyes) or only shallowly open (two eyes) in the control eyes. No corneal epithelial defects or conjunctival wound leaks were detected during the postoperative course. One 5-fluorouracil–treated eye (the same eye noted to have had a posteriorly located internal trabeculectomy ostium) had suspended red blood cells in the anterior chamber (no layered hyphema) at the one-week postoperative examination only. Two eyes in each group had anterior subcapsular lens opacities (one trace and one mild in the 5-fluorouracil–treated group; two mild in the control group) at the six-week postoperative examination (Table 2).

A mononuclear and foreign body giant cell reaction was present in the periphery of the collagen implants in both groups (Figs. 1 to 3). Based on estimates of the maturation sequence, the reaction appeared to have begun in the periphery of the collagen implants and extended centrally; in the 5-fluorouracil–treated eyes (Figs. 1 and 2), the reaction was either inhibited or simply delayed, relatively sparing the central portion of the implants.

TABLE 2
CLINICAL FINDINGS AND COMPLICATIONS

	5-FLUOROURACIL–TREATED EYES	CONTROL EYES
Filtering bleb (6 wks postoperatively)		
Absent	2	3
Small	0	1
Moderate	2	0
Large	0	0
Gonioscopy of trabeculectomy site (6 wks postoperatively)		
Occluded by peripheral anterior synechiae	1	0
Filled in	0	2
Shallowly open	0	2
Deeply open	3	0
Complications		
Corneal epithelial defect	0	0
Conjunctival wound leak	0	0
Hypotony	2 (transient)	0
Insignificant hyphema	1 (transient)	0
Cataract		
None	2	2
Trace anterior subcapsular	1	0
Mild anterior subcapsular	1	2

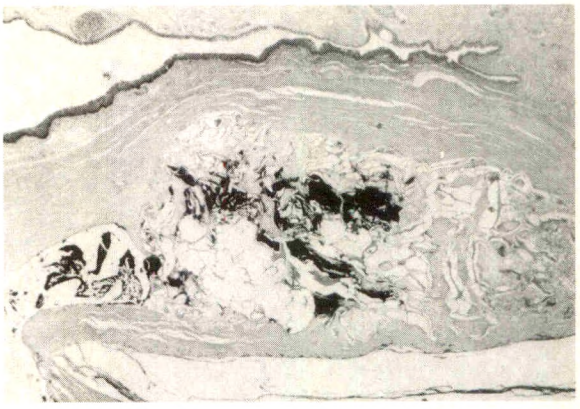

Fig. 1 (Hasty, Heuer, and Minckler). Scleral fistula adjacent to 5-fluorouracil collagen implant. Apparent patency of fistula is demonstrated by presence of India ink within central portion of collagen implant. Anterior edge of collagen implant appears to have acted as scaffold for partial fibrous obliteration of the external side of scleral fistula (hematoxylin and eosin, ×31.25).

Fibroblasts diffusely infiltrated the interstices of the collagen implants. The fibroblastic response in the 5-fluorouracil–treated eyes (Fig. 2) was less marked, with less dense extracellular matrix, than in the control eyes (Fig. 3).

The anterior chamber India ink marker infiltrated the collagen implants in most eyes, but was partially blocked by the fibroblastic response, which used the collagen matrix of the implants as a scaffold along the posterior edge of the fistula (Figs. 1 and 2).

Focal necrosis with surrounding mononuclear cell infiltrate was noted in the subconjunctival tissues of all eyes 180 degrees from the collagen implants at the site of subconjunctival triamcinolone injection.

Discussion

Failures of filtering surgery are usually attributable to postoperative scarring, a process in which fibroblasts play a prominent role. Subconjunctival administration of 5-fluorouracil to inhibit fibroblast proliferation after filtering surgery has achieved relatively widespread application among glaucoma specialists and has been the subject of a National Eye Institute–sponsored clinical trial. The one-year results of

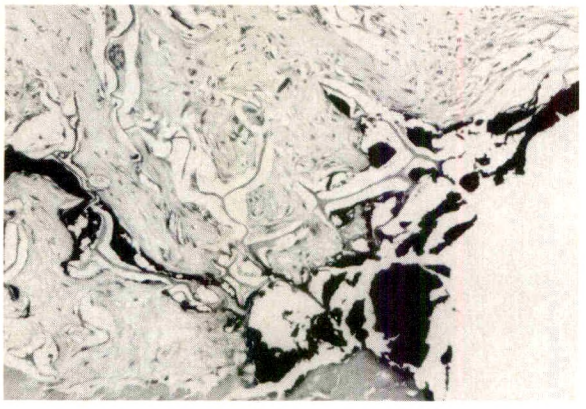

Fig. 2 (Hasty, Heuer, and Minckler). Another 5-fluorouracil collagen implant with plane of section including fistula into anterior chamber. Inflammatory response, which includes numerous foreign body giant cells and fibroblasts, diffusely infiltrates peripheral portions of collagen implant. India ink, which was injected intracamerally before the monkeys were killed, shows patency between central portion of collagen implant and anterior chamber. Particles of India ink and fibrous tissue, including multinucleated giant cells, surround beams of collagen implant. Surface of implant appears to have provided scaffold for partial fibrous obliteration of external opening of scleral fistula (hematoxylin and eosin, × 400).

Fig. 3 (Hasty, Heuer, and Minckler). Area near central portion of control collagen implant shows interface between completely occluded area with intense foreign body giant cell reaction and relatively open area that includes India ink. Interstices of collagen implant stand out clearly as noncellular structures (hematoxylin and eosin, × 400).

that clinical trial demonstrated a significantly (P = .0007, Mantel-Haenszel chi-square) lower failure rate with postoperative subconjunctival 5-fluorouracil in patients with poor surgical prognoses.[1] To avoid the inconvenience and discomfort of subconjunctival injections, topical administration has also been studied[5]; subconjunctival and topical administration of 5-fluorouracil, however, both cause corneal epithelial toxicity and both achieve higher 5-fluorouracil concentrations in ocular tissues other than in the subconjunctival space at the filtering site.

A sustained-release delivery system for 5-fluorouracil that could be implanted during filtering surgery would allow administration of a lower total 5-fluorouracil dose while achieving a more consistently therapeutic 5-fluorouracil concentration within the filtering bleb. Potential disadvantages of sustained-release administration of 5-fluorouracil are the possibility of increased conjunctival toxicity (conjunctival wound or buttonhole leaks) immediately over the delivery system itself and the possibility of an inflammatory response to the delivery system. (Subconjunctival injection of triamcinolone has been shown to cause a mononuclear cell infiltrate, fibroblastic proliferation, and collagen deposition around the injection site[6]; in this study, marked focal necrosis with surrounding mononuclear cell infiltrate in the subconjunctival tissues was observed at the sites of the triamcinolone injections.)

In our study, a marked multinucleated foreign body giant cell reaction occurred in response to the collagen implant. Foreign body giant cells, epithelioid cells, and mononuclear cells were abundant in the periphery of all sponges. 5-Fluorouracil only decreased (or merely delayed) the reaction in the central portion of the implants. Furthermore, the collagen columns of the implants acted as scaffolds for fibroblast infiltration.

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OPHTHALMIC MINIATURE

They don't see us coming because they don't see much of anything. Ironically, despite their superabundance of eyes, most scorpions seem to be almost hopelessly blind. Scientists who study scorpion biology generally mention this handicap ("The eyes are too crude to be of much assistance . . . . The eyesight seems to be of secondary importance . . . . Scorpions have poor eyesight"), which is so pronounced, evidently, that it has been a mystery how scorpions could ever find their way to a meal.

David Quammen, *The Flight of the Iguana*
New York, Delacorte Press, 1988, pp. 45 and 46

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PERSPECTIVES

Mitochondria and Leber's Hereditary Optic Neuropathy

Nancy J. Newman, M.D., and Douglas C. Wallace, Ph.D.

Over the last decade, the application of molecular genetics to the analyses of hereditary metabolic diseases has resulted in extraordinary progress in every medical specialty. Major advances in the molecular biology of the eye include the isolation of the retinoblastoma gene,[1] the clarification of X-linked color vision abnormalities,[2] the mapping of retinitis pigmentosa genes[3] with identification of one responsible mutation in the rhodopsin gene,[4] and the identification of mutations of the ornithine aminotransferase gene that cause gyrate atrophy.[5,6]

Most molecular genetic studies have focused on the nuclear genome. Recently, however, Leber's hereditary optic neuropathy has been shown to be the result of a mutation in the extranuclear mitochondrial deoxyribonucleic acid (mtDNA).[7-9]

The mitochondrial DNA molecules are located within the hundreds of mitochondria in the cytoplasm. The mitochondria generate most of the cellular energy and provide approximately 90% of the total adenosine triphosphate used by humans.[10,11] Some cells and tissues are more reliant on mitochondrial adenosine triphosphate than others. The central nervous system is the most dependent, followed by the cardiac conduction system, oxidative skeletal muscle, kidneys, and liver.

See also p. 625.

The cytoplasm of each cell contains thousands of virtually identical mitochondrial DNA molecules, approximately 0.3% of the cell's total DNA, with each mitochondrion containing between two and ten double-stranded mitochondrial DNA molecules.[11-13] Like nuclear

DNA, mitochondrial DNA is read onto messenger ribonucleic acids (mRNA), which are then translated into proteins by ribosomes. The entire process takes place within the mitochondrion. Hence, the mitochondrion encompasses all of the molecular machinery of a bacterium, suggesting that the mitochondria were once free-living oxidative bacteria that entered into a symbiotic relationship with the glycolytic protoeukaryotic cell.[10]

The mitochondrial DNA is distinctive in several ways. Its genetic code is slightly different from the "universal" genetic code of the nucleus, its genes lack the introns and other noncoding sequences frequent in nuclear genes, and it is replicated and generates mature mitochondrial RNA in a manner unlike that of nuclear DNA.[10,11,13]

The mitochondrial DNA molecule codes for the ribosomal RNA (rRNA) and transfer RNA (tRNA) used in mitochondrial protein synthesis as well as for 13 essential subunits of the mitochondrial energy-production system, oxidative-phosphorylation.[10-13] The remainder of the oxidative-phosphorylation subunits are encoded by the nucleus. The mitochondrial DNA components include seven subunits of complex I (reduced nicotinamide adenine dinucleotide [NADH] dehydrogenase), one subunit of complex III (ubiquinol-cytochrome c oxidoreductase), three subunits of complex IV (cytochrome c oxidase), and two subunits of complex V (adenosine triphosphate synthase).[10-12] Hence, mutations in the human mitochondrial DNA can lead to diseases caused by energy deficiency.

The mitochondrial DNA has a unique inheritance pattern; it is inherited exclusively from the mother.[14,15] During sexual reproduction, the cytoplasmic contents (including the entire complement of mitochondria) are provided by the mother's ovum. The father's sperm cytoplasm is lost. Therefore, offspring inherit only their mother's mitochondrial DNA. Mitochondrial DNA replicates within the mitochondrion, and the mitochondria divide asymmetrically without regard to mitochondrial DNA content or timing of replication.[10,11] When new mutations in the mitochondrial DNA occur, there is a period of mixed intracellular populations of mutant and normal mitochondrial DNA molecules (heteroplasmy). At each cytokinesis of a heteroplasmic cell, the inclusion of the mutant and normal mitochondrial DNA molecules within the daughter cells is random. Hence, during mitotic or meiotic replication, the proportion of mutant and normal mitochondrial DNA can drift by a process called replicative segregation.[10-12] Because the mitochondrial DNA encodes only energy genes, the reduction in cellular energy production should be directly proportional to the number of mutant mitochondrial DNA molecules in the cell.

Leber's hereditary optic neuropathy is characterized by familial transmission of subacute, sequential, bilateral central visual loss that occurs mainly in young men.[16-23] The clinical entity has been recognized since the early 19th century.[16,17,20] The onset of visual dysfunction is usually between ages 18 and 30 years, but there are many examples of younger and older patients.[18,20-23] There is a male predominance, ranging from 60% to 90%.[19,20,22,23] Central vision deteriorates progressively, first in one eye and then in the other, typically after an interval of days to weeks. Intervals of up to eight years have been reported.[20] There are few, if any, associated symptoms at the time of visual loss, although a transient worsening of visual function with exercise or warming as occurs in other optic neuropathies (Uhthoff's symptom) is not uncommon.[20,24,25] All levels of visual acuity loss have been documented, but most visual acuities ultimately deteriorate to worse than 20/200 in each eye, usually over several weeks to one or two months.[19-21] Color vision is affected early, and the visual fields demonstrate central or cecocentral defects.[20,25,26]

In 1973, Smith, Hoyt, and Susac[24] described the typical ophthalmoscopic features of acute Leber's optic neuropathy: circumpapillary telangiectatic microangiopathy, swelling of the nerve fiber layer around the optic disk (pseudoedema), and absence of leakage on fluorescein angiography (as opposed to the disk leakage expected in true disk edema). This early ophthalmoscopic picture may not be seen by the physician, and only optic atrophy with nerve fiber layer loss most prominent in the papillomacular bundle may remain.[20,21,23,25] Most patients with Leber's optic neuropathy do not recover useful vision. Reports of patients with partial or even complete visual recovery even five to ten years after onset, however, are surprisingly numerous.[20,27]

Visual dysfunction is the only manifestation of the disease in most patients. There is evidence, however, of some association with other neurologic abnormalities, such as exaggerated or pathologic reflexes, cerebellar ataxia, or peripheral neuropathy.[18] Perhaps best established is the link between Leber's optic neuropathy

and cardiac conduction abnormalities, specifically pre-excitation syndromes.[23] Associated skeletal abnormalities have also been reported.[20] Hereditary optic neuropathies similar to Leber's have also been reported in association with Charcot-Marie-Tooth disease (a hereditary disease of peripheral nerves) in at least two families,[28,29] with early onset dystonia and basal gangliar lesions,[30,31] and with strokelike episodes and other neuropsychiatric disorders.[32] These syndromes may have different molecular causes.

It has long been recognized that the inheritance of Leber's optic neuropathy does not follow mendelian principles.[19,20,22,23,26,33,34] Genealogic studies that used optic nerve dysfunction as the marker of the disease suggested carrier rates of between 50% and 96%.[20,23] In the most extensive review of Leber's optic neuropathy to date, Nikoskelainen and associates[23] helped to establish Leber's optic neuropathy as an example of true maternal inheritance. They investigated four Finnish pedigrees, including as a marker for the disease the ophthalmoscopic abnormality of peripapillary microangiopathy, and concluded that every son or daughter of a female carrier inherited the Leber's trait. Theories of slow viruses transferred transplacentally or within the maternal ooplasm have been essentially replaced by attention to the mitochondria.

In 1988, Wallace and associates[7] identified a mitochondrial replacement mutation in nine of 11 families with members diagnosed with Leber's hereditary optic neuropathy. A single nucleotide change at position 11778 in the mitochondrial DNA converts the highly conserved codon 340 of NADH dehydrogenase subunit 4 from an arginine to a histidine. NADH dehydrogenase is the first enzyme in the electron transfer pathway of oxidative phosphorylation. Parker, Oley, and Parks[35] found reduced activity of this complex in the platelets of patients with a more severe disease that combines a bilateral optic atrophy that is like Leber's with a variety of other neurologic defects.

The Leber's mutation eliminates a restriction endonuclease site in the patient's mitochondrial DNA, thereby providing a simple method for determining the presence of the mutation as a restriction-fragment–length polymorphism.[7,8] Maternally related members of these families carry the mitochondrial DNA mutation, regardless of phenotypic expression. Vilkki, Savontaus, and Nikoskelainen confirmed the presence of this mutation in ten of 19 Finnish families.[9]

Although many cases of Leber's hereditary optic neuropathy are associated with large pedigrees,[18,19,23,26] many additional cases with the classic manifestations of the disease seem to appear sporadically. It is therefore unclear whether these are new mutations or if all Leber's patients are related through asymptomatic carriers. The identification of Leber's hereditary optic neuropathy in an American black pedigree permitted this problem to be studied. If all Leber's patients were related through a common founding mother, then all Leber's patients with the 11778 mutation should have the same associated mitochondrial DNA markers. However, Singh, Lott, and Wallace[8] found that the mitochondrial DNA molecules of the American black and European Leber's patients were as divergent as these racial groups. Hence, the Leber's mutation must have appeared at least twice independently, once on each mitochondrial DNA background. This contention is supported by the demonstration of the 11778 mutation in Asian patients as well.[36]

Because each human cell has thousands of mitochondrial DNA molecules, a new mutation must become progressively enriched from one mutant molecule in thousands of normal molecules, through an equal proportion of mutant and normal mitochondrial DNA molecules, to virtually pure mutant mitochondrial DNA. It is likely that many new mutant mitochondrial DNA molecules are randomly lost and only a few predominate sufficiently to cause demonstrable disease. Elsewhere in this issue,[37] some unaffected family members of supposedly isolated Leber's patients are shown to be strongly heteroplasmic, containing both normal and mutant mitochondrial DNA molecules in their tissue samples. Furthermore, in one family, the proportion of mutant mitochondrial DNA molecules had progressively increased from grandmother to mother to blind son. It seems likely that we are witnessing the progression that occurs during the fixation of a mitochondrial DNA mutant. Because many sporadic cases of the disease occur in patients who have heteroplasmic unaffected maternal relatives, it is possible that many supposedly sporadic Leber's cases may be the result of a mutation that has become sufficiently enriched by mitotic segregation to result in clinical disease.

It remains difficult to explain why all individuals with predominantly mutant mitochondrial DNA molecules as measured in their blood do

not lose their vision. One reason suggested relates to the finding that different tissues within a heteroplasmic individual can have widely different proportions of mutant mitochondrial DNA molecules.[37] Hence, some family members with predominantly abnormal blood might have predominantly normal mitochondria in their optic nerves.

Variable heteroplasmy in somatic tissues, however, cannot be the only answer. The mutation itself is not sufficient to cause blindness, because patients with Leber's disease are born essentially homoplasmic for the mutation yet do not lose their vision until later in life. One hypothesis is that the delayed expression of the mutation results from a respiratory defect that is not complete. Energy production of the optic nerve is reduced but not eliminated. As long as there is sufficient mitochondrial adenosine triphosphate to run the cellular pumps, the nerve will conduct action potentials and the individual will see. If there is insufficient energy for all the cellular requirements, however, there will be inhibition of the functions that repair and maintain the cell, such as DNA and RNA synthesis and protein turnover. The damage may be cumulative during life, with phenotypic expression (that is, a rapid loss of vision) resulting when sufficient optic nerve cells die.

If this hypothesis is correct, genetic and environmental factors that exacerbate this energy deficiency would be expected to increase the probability of optic neuropathy. Male gender may be one of these factors. Anoxia from smoking, exposure to respiratory inhibitors such as cyanide, rotenone, or environmental toxins, or even nutritional deficiencies might also increase the expression of the disease. It is possible that reduction of respiratory stress could reduce the number of mutation-positive patients who lose their vision.

The demonstration of heteroplasmy in Leber's patients and the discovery that the proportion of mutant and normal mitochondrial DNA molecules can shift rapidly during both meiotic and mitotic replication make it clear that genetic counseling of Leber's patients will be improved by analysis of the mitochondrial DNA genotype in not only blood, but in other available cell sources, such as hair, buccal mucosa, and urinary tract epithelia. Additionally, genetic counseling of other family members will require a careful genotypic analysis of each. Although the resulting genetic situations are complex, this complexity offers hope for maternal lineage relatives who would otherwise be condemned to suffer Leber's hereditary optic neuropathy as a consequence of the rules of maternal inheritance. Hence, the hope and challenge for counseling and prevention is to develop better methods for assessing heteroplasmy and to find new methods of reducing respiratory stress and enhancing respiratory output.

From the Departments of Ophthalmology (Dr. Newman), Neurology (Drs. Newman and Wallace), and Biochemistry and Pediatrics (Dr. Wallace), Emory University School of Medicine, Atlanta, Georgia. This study was supported in part by a departmental grant from Research to Prevent Blindness, Inc. (Dr. Newman), and by National Institutes of Health grant N521328 and a Muscular Dystrophy Clinical Research grant (Dr. Wallace).

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LETTERS TO THE JOURNAL

Suprachoroidal Dislocation of a Posterior Chamber Intraocular Lens

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In traumatic dislocation of a posterior chamber intraocular lens after cataract surgery, the posterior chamber intraocular lens may be dislocated subconjunctivally,[1] into the vitreous cavity,[2] or, in extreme cases, completely extruded from the eye.[3] We treated a patient who had a posterior chamber intraocular lens that dislocated into the suprachoroidal space.

A 57-year-old woman had decreased vision after being struck in the left eye by a clothes hanger. She had undergone an uncomplicated extracapsular cataract extraction with implantation of a posterior chamber intraocular lens in her left eye five weeks previously. The haptics of the intraocular lens were placed in the ciliary sulcus. Visual acuity was L.E.: 2/200 with an intraocular pressure of 8 mm Hg. The surgical incision at the superior corneoscleral limbus was intact, with a formed anterior chamber. The intraocular lens was displaced superiorly, compressing the superior haptic against the iris into the ciliary sulcus. The superior vitreous was prolapsed around the lens optic. Examination of the fundus showed a suprachoroidal mass with a sharp profile and a curvilinear configuration. The mass began at the 10 o'clock meridian in the pars plana region and extended circumferentially and posteriorly around the disk to lie below the inferotemporal retinal vascular arcade (Figs. 1 and 2). No retinal tears, retinal detachment, or choroidal hemorrhages were seen. Suprachoroidal dislocation of the inferior haptic was suspected.

A pars plana vitrectomy was performed. After all the vitreal and capsular attachments to the intraocular lens were removed, the lens was

Fig. 1 (Foster and associates). A sharply defined curvilinear suprachoroidal mass (inferior lens haptic) coursing posteriorly through the superonasal quadrant.

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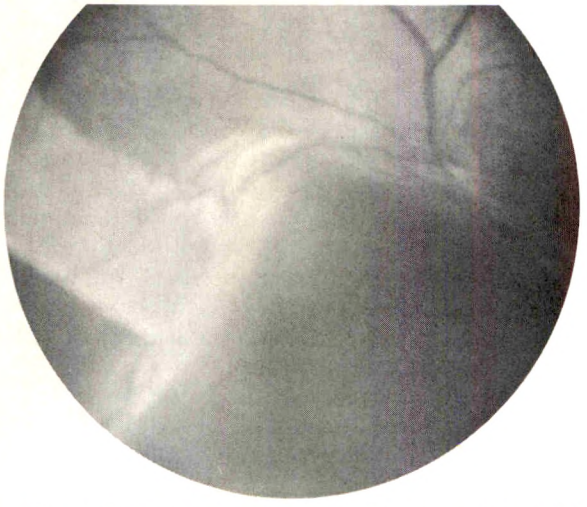

Fig. 2 (Foster and associates). The suprachoroidal mass (inferior lens haptic) curving around the disk to the inferotemporal retinal vascular arcade.

rotated into the anterior chamber using two Sinsky hooks, thus removing the inferior haptic from the suprachoroidal space. Since the remaining capsule and zonules were inadequate to support the intraocular lens, it was removed from the eye through the original limbal incision. The presumed pars plana entry site of the inferior haptic could not be seen with indirect ophthalmoscopy and scleral depression. No retinal breaks, hemorrhages, or detachment were seen. Gonioscopy disclosed no cyclodialysis cleft. Three months postoperatively, the best-corrected visual acuity was L.E.: 20/40.

A similar case involving an anterior chamber intraocular lens has been reported.[4] In that patient, the anterior chamber lens was displaced between the sclera and the ciliary body through a traumatic cyclodialysis cleft. In our patient, we believe that the blunt trauma to the eye resulted in the optic and the superior haptic being compressed superiorly, with subsequent capsular disruption and vitreous prolapse. The inferior haptic, which initially moved superiorly, recoiled inferiorly after the impact. The tip of the inferior haptic may have torn and dissected under the ciliary epithelium of the pars plana. Following its curvature, the inferior haptic then came to rest in the suprachoroidal space. The placing of the inferior haptic of the intraocular lens in the ciliary sulcus may have predisposed its dislocation into the suprachoroidal space after trauma.

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Traumatic Rupture of the Globe After Glaucoma Surgery

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After blunt trauma, the normal eye usually ruptures at the corneoscleral limbus or at the recti muscles where the sclera is thin.[1] The common site of rupture after blunt trauma in a globe that has had previous surgery appears to be at the site of surgical incision. This has been reported to occur after cataract surgery,[2] penetrating keratoplasty,[3] and radial keratotomy,[4] often years after the initial operation. We repaired four globes that had ruptured two to six years after trabeculectomy or trabeculectomy combined with cataract extraction and intraocular lens implantation.

A 57-year-old man was severely beaten on the head and face six years after a trabeculectomy was performed on the right eye for chronic open-angle glaucoma. After the injury, visual acuity was R.E.: light perception with projection and L.E.: 20/400. The patient had a pinpoint pupil in the right eye after treatment with pilocarpine eyedrops and traumatic mydriasis in the left eye. Both pupils appeared nonreactive, and it was impossible to detect an afferent pupillary defect. Penlight examination showed swollen, ecchymotic eyelids and subconjuncti-

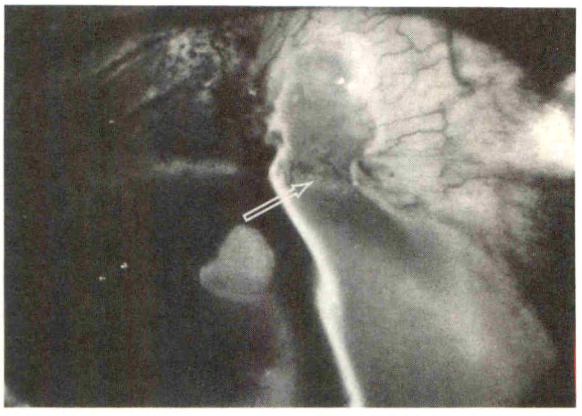

Figure (Zeiter and Shin). Positive Seidel test at the trabeculectomy site of the superior corneoscleral limbus in the right eye (arrow).

val hemorrhages in both eyes. The right eye had a small conjunctival laceration 3 mm temporal to the corneoscleral limbus and a flat bleb superiorly. The cornea was clear in both eyes and a small hyphema was apparent in the right eye. Intraocular pressure was R.E.: 2 mm Hg and L.E.: 27 mm Hg. A Seidel test showed leakage of the aqueous humor at the trabeculectomy site of the right eye (Figure). Examination of the fundus showed a diffuse vitreous hemorrhage in the right eye and a cup/disk ratio of 0.8 in the left eye.

The patient was taken to the operating room. A 2-mm scleral laceration extending posteriorly from underneath the lamellar scleral flap was noted. This scleral rupture and the overlying conjunctival laceration were repaired with 7-0 Vicryl suture. Visual acuity three weeks after the injury was R.E.: hand motions and L.E.: 20/100.

In two similar patients, scleral lacerations were found to extend from the limbal incision of a combined cataract extraction, posterior chamber intraocular lens implantation, and trabeculectomy. The intraocular lenses in these two patients were partially expulsed, causing one of the haptics to protrude through the scleral flap to the subconjunctival space. Dislocation, expulsion, and even fracture of intraocular lenses have been reported in pseudophakic eyes after cataract extraction.[5] A fourth patient had complete wound dehiscence of the triangular scleral flap with a haptic of a posterior chamber intraocular lens protruding through it into the subconjunctival space after blunt trauma in an eye that had a combined trabeculectomy, phacoemulsification, and small incision intraocular lens implantation.

The scleral flap heals after trabeculectomy by ingrowth of fibroblasts and bridging of collagen, which accounts for a tensile strength that is less than that of uninjured sclera, even years after surgery.[2] Wound healing after trabeculectomy is often suppressed by topical corticosteroid use or by 5-fluorouracil injection to maintain a patent filtering fistula. Such inhibition of fibroblast proliferation may leave the sclera even more susceptible to rupture after blunt trauma. Patients who have had a glaucoma filtering surgery, with or without combined cataract surgery, are less resistant to blunt trauma and may be in need of protective spectacles.

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Visual Loss From Endothelial Cell Melanization of the Cornea

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Corneal endothelial cells have the capacity to phagocytose free melanin granules circulating

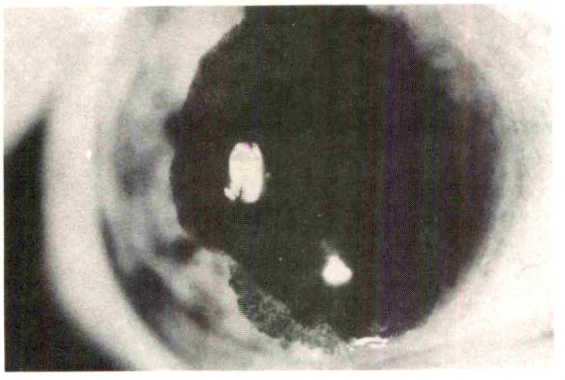

Fig. 1 (Mosteller and Margo). A dense retrocorneal layer of brown pigment prevents visualization of the anterior chamber. The membrane is surrounded by clear cornea.

in the aqueous humor. Anterior segment trauma and inflammation are the most common causes of pigment dispersion. Secondary melanization of corneal endothelial cells rarely becomes severe enough to interfere with vision. We treated a patient who developed dense endothelial cell pigmentation that resulted in substantial visual loss.

An 82-year-old woman had undergone bilateral intracapsular cataract extraction 15 years previously. She had been successfully wearing aphakic spectacles for several years when she noted blurred vision in her right eye. Vision in the right eye progressively declined over the next ten years because of the accumulation of pigment on the posterior surface of the cornea. The patient was referred for penetrating keratoplasty when her visual acuity declined to R.E.: 20/400.

On ocular examination, a dense layer of pigment on the posterior surface of the cornea precluded adequate visualization of the anterior chamber and posterior segment of the right eye (Fig. 1). The pigment was surrounded by clear cornea. There was a sector iridectomy at the 12 o'clock meridian with some prolapse of vitreous into the anterior chamber. The vitre-

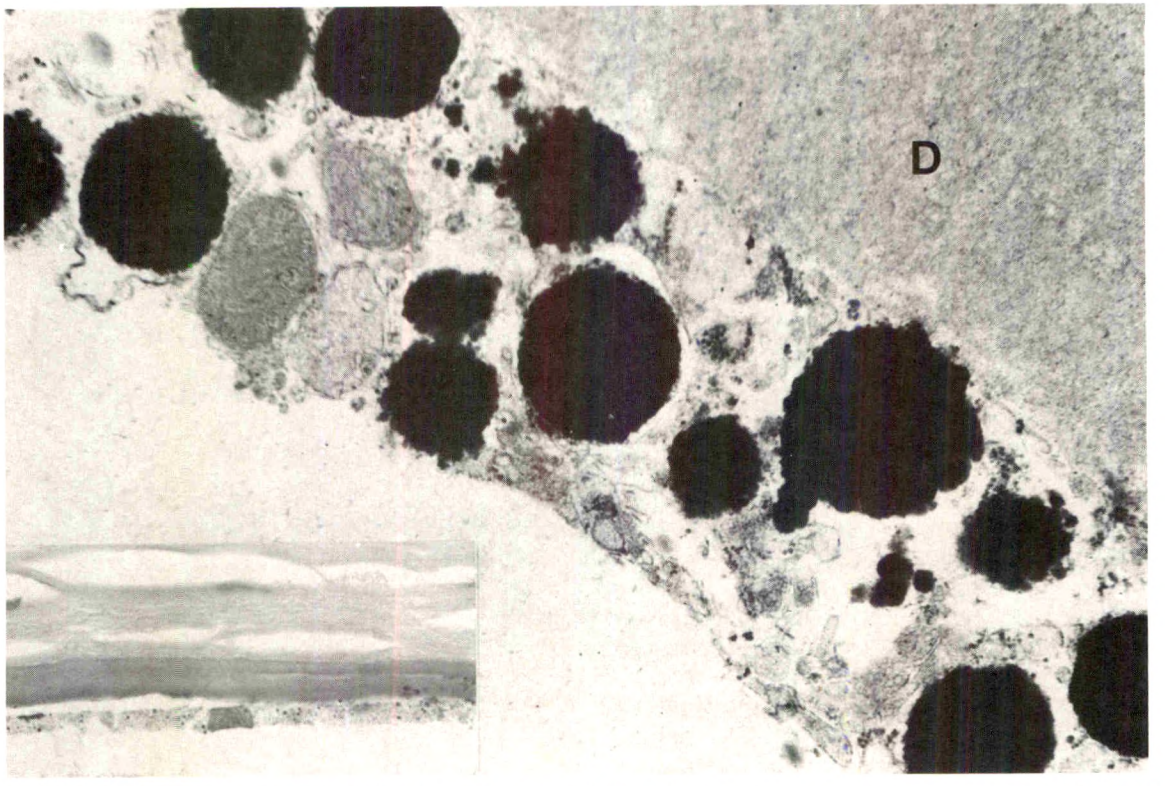

Fig. 2 (Mosteller and Margo). Endothelial cells are packed with melanin granules measuring up to 1.4 μm in diameter. Descemet's membrane (D) is normal (× 21,600). Inset, bleached section shows typical endothelial cell structure (hematoxylin and eosin, × 440).

ous was not adherent to the cornea. There was no corneal edema. The left cornea was normal.

Histologic examination of the corneal button after keratoplasty showed endothelial cells packed with melanin granules (Fig. 2, inset). Descemet's membrane was normal. Ultrastructural studies showed single melanin granules in lysosomes, measuring between 0.7 and 1.4 μm in diameter (Fig. 2). Melanized cells were identical by light (bleach section) and electron microscopy to normal endothelial cells at the periphery of the button except for the presence of melanin.

Confluent melanization of endothelial cells is rare. This phenomenon was not observed among 200 cases of pigmented retrocorneal membranes reported by Kampik, Patrinely, and Green,[1] although 27% of the membranes in the study were composed predominantly of endothelial cells. Bloomfield and Gray[2] described a man whose vision was affected by dense pigmentation of endothelial cells in a corneal graft. The diagnosis was confirmed histologically. The graft was originally performed to treat an alkali injury. The heavy accumulation of melanin granules in endothelial cells did not appear to have any adverse effects on endothelial cell function, since there was no evidence of edema in the graft.

Jerrold and Shapiro[3] reported a densely pigmented retrocorneal membrane that had a "honeycombed" pattern on slit-lamp examination, consistent with melanization of endothelial cells. The membrane developed ten years after cataract surgery had been performed. The histogenesis of the membrane is speculative, however, since the cornea was not examined histologically.

It appears that dense, confluent melanization of endothelial cells alone can impair vision, yet not have an adverse effect on endothelial cell function.

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Interface Abscess After Epikeratoplasty

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Common complications of epikeratoplasty include chronic epithelial defects, dehiscence of the lenticule, lenticular haze, and failure to achieve the desired visual result.[1-3] Lenticular infections involving the stroma of the lenticule or the graft-host interface are rare and usually require removal of the graft to protect the recipient cornea.

An 80-year-old woman had decreased vision, redness, and irritation in her left eye. She was referred to one of us (A.M.B.) for treatment. The patient had undergone a complicated cataract extraction 17 months previously in her left eye without insertion of an intraocular lens. An uncomplicated epikeratoplasty had been performed in the left eye four months previously. Several but not all of the sutures had been removed electively.

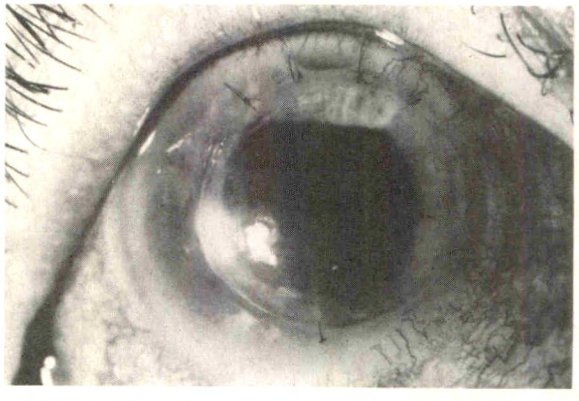

Figure (Hemady, Bajart, and Wagoner). Interface abscess after epikeratoplasty one day after removal of the 10-0 nylon suture overlying the abscess.

Visual acuity was L.E.: hand motions. Well-circumscribed, localized infiltrates were noted in the peripheral lenticule-host interface at the 8 o'clock meridian with lenticular edema involving the visual axis (Figure). The infiltrates did not appear to extend into the recipient cornea. Four intact and two loose 10-0 nylon sutures were present, one overlying the abscess. A 4-mm hypopyon was present in the anterior chamber.

The suture overlying the abscess was removed and cultured, and the abscess was scraped for culture with a No. 15 blade. Intensive topical vancomycin hydrochloride was given, and prednisolone acetate 1% was added two days later. Cultures grew coagulase-negative *Staphylococcus* species. Seven days after initiation of therapy, visual acuity was L.E.: counting fingers at one foot with marked clearing of the abscess and the hypopyon. The remaining sutures were removed. Vancomycin hydrochloride was discontinued after 14 days. One month later best-corrected visual acuity was L.E.: 20/80 with a clear lenticule centrally and mild residual haze without infiltrates at the 8 o'clock meridian.

The interface abscess of our patient is an unusual complication after epikeratophakia. The prolonged retention of sutures (three months) probably was the inciting factor for the development of the abscess. We recommend that all sutures be removed three weeks after an epikeratoplasty for pediatric aphakia and eight weeks after epikeratoplasty for adult aphakia. If a graft or graft-host abscess develops in the visual axis, the graft should be removed immediately. Examination and therapy should then be initiated. If the infectious process is peripheral, conservative management may be attempted, but if any extension of the infection occurs, removal of the graft should be considered.

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Invasive Conjunctival Tumor With Keratoacanthoma Features

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Keratoacanthoma rarely occurs in the conjunctiva.[1-3] Clinical features that suggest the diagnosis of keratoacanthoma include rapid onset and enlargement (days to weeks). The principal clinical and histopathologic entity in the differential diagnosis of keratoacanthoma is squamous cell carcinoma. In contrast, squamous cell carcinoma forms over months to years, and intraocular invasion of conjunctival squamous cell carcinoma has been reported.[4] We treated a patient who had the clinical and histopathologic features of a conjunctival keratoacanthoma that recurred and showed intraocular invasion.

A 65-year-old man was examined for irritation of his left eye. Two weeks previously, the patient noted the appearance of a small, white elevation at the left temporal corneoscleral limbus that rapidly expanded. He was certain that no such lesion had existed before that time. Examination showed a white, firm, fixed, nontender mass with a central crater apparent at the left temporal corneoscleral limbus. The mass initially measured 5 × 3 × 3 mm; one week later it measured 6.5 × 5 × 4 mm (Fig. 1). Excisional biopsy showed a crater-shaped epithelial neoplasm bounded by a rim of normal conjunctival epithelium. The crater contained keratin, and individual neoplastic epithelial cells had abundant, pale, eosinophilic cytoplasm. The neoplasm extended to the deep margin of resection. Keratoacanthoma was diagnosed. The lesion recurred ten weeks postoperatively, and excisional biopsy showed similar histopathologic features with the initial speci-

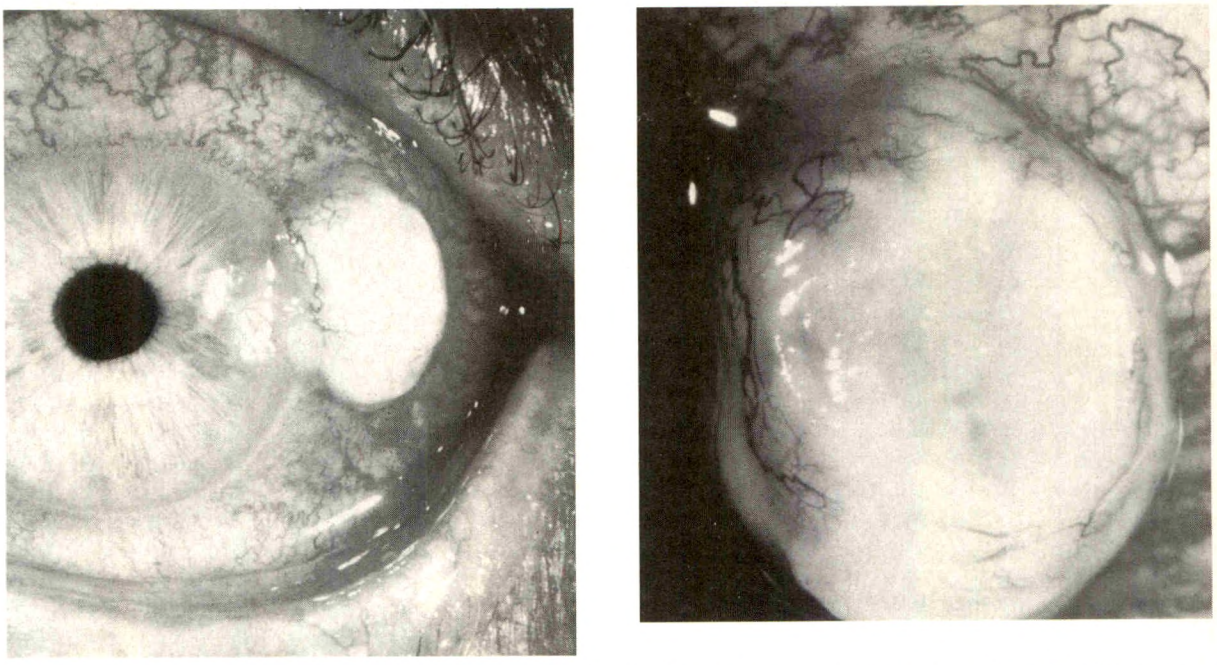

Fig. 1 (Grossniklaus, Martin, and Solomon). Left, A raised epibulbar mass consisting of a white keratinous plug surrounded by hyperemic conjunctiva is apparent at the corneoscleral limbus temporally. Right, Close inspection discloses that hyperemic conjunctiva surrounds a crater of white keratinous material.

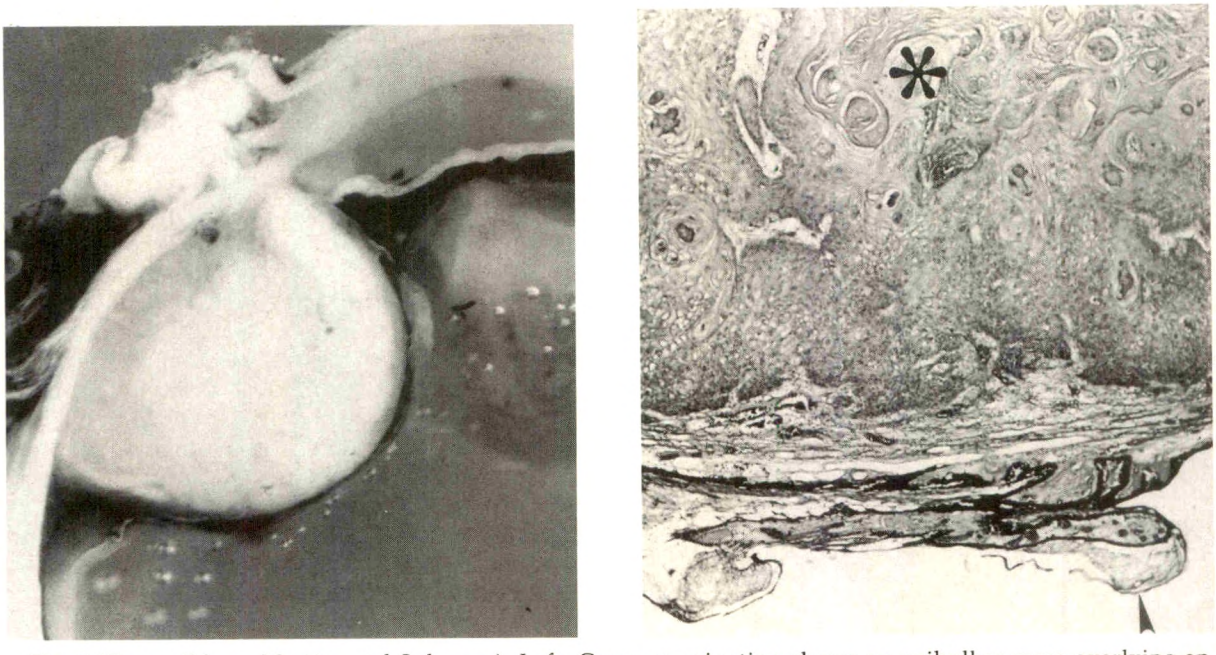

Fig. 2 (Grossniklaus, Martin, and Solomon). Left, Gross examination shows an epibulbar mass overlying an intraocular mass of similar color and consistency. Right, The intraocular portion of the tumor is composed of a coherent mass of cells surrounding a keratinous center (asterisk). The pars plicata (arrowhead) has been displaced and distended by the tumor (hematoxylin and eosin, × 10).

men. One month postoperatively the lesion again recurred, and was 1.5 × 1.5 × 1.5 mm. The lesion grew to 4 × 4 × 4 mm in one week. Gonioscopy disclosed intraocular invasion with involvement of the angle. After discussing various treatment options, we enucleated the eye. Examination of the enucleated eye showed intraocular invasion of the epibulbar tumor (Fig. 2). The tumor was cohesive and had histopathologic features similar to those of the initial lesion and first recurrence, namely epithelial cells with waxy, eosinophilic cytoplasm surrounding a central, keratin-filled core.

The clinical history, craterform histologic architecture, and cytologic features in our patient are consistent with a diagnosis of keratoacanthoma, although the invasiveness suggests squamous cell carcinoma. The intraocular, well-demarcated mass is unlike the diffuse infiltrative involvement of squamous cell carcinoma of the conjunctiva.[4] Keratoacanthoma has been shown to have dermal invasion in some instances.[5] Although some pathologists argue that squamous cell carcinoma can originate from keratoacanthoma, it is likely that these neoplasms are squamous cell carcinoma, which closely mimics the histologic features of keratoacanthoma rather than carcinoma ex keratoacanthoma.[5]

The pathogenesis of intraocular invasion in our patient is unknown. Possibly mechanical trauma introduced the epibulbar neoplasm into the eye or the tumor invaded through an emissary canal. Perineural invasion has been reported in association with keratoacanthoma, and perhaps perineural invasion through an emissary canal occurred in our patient.

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Infectious Crystalline Keratopathy Caused by *Mycobacterium fortuitum* and *Pseudomonas aeruginosa*

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Infectious crystalline keratopathy is characterized by a slowly progressive, white refractile anterior stromal infiltrate found in patients receiving long-term corticosteroid therapy. *Streptococcus viridans* has been identified as the cause in most of the reported cases.[1] We treated a patient with infectious crystalline keratopathy caused by *Mycobacterium fortuitum* and *Pseudomonas aeruginosa*.

A 30-year-old woman had a bacterial corneal ulceration of the right eye 14 years previously that resulted in a dense, central corneal scar. She underwent penetrating keratoplasty with 16 interrupted sutures in December 1988. Postoperative medications included betamethasone and antibiotic eyedrops. All sutures were removed in August 1989, except for two broken stitches at the 7 o'clock and 8 o'clock meridians. The patient had mild pain without redness in October 1989. Betamethasone was used without improvement. The patient returned to our clinic one week after the episode. A white, refractile stromal infiltrate with anterior one-sixth stromal loss was found at the graft-host junction surrounding the broken stitch at the 8 o'clock meridian (Fig. 1). A scraping of the ulcer showed numerous acid-fast bacilli and a few gram-negative bacilli. Corneal cultures grew *M. fortuitum* and *P. aeruginosa*. Betamethasone was discontinued and topical amikacin and carbenicillin were instituted. The infiltrate became confluent with progressive stromal melting and endothelial plaque formation despite treatment (Fig. 2). Systemic amikacin and carbenicillin were added two weeks later because of impending scleral involvement. The corneal infiltrate, endothelial plaque, and anterior chamber reaction slowly resolved. Repeated bacteriologic studies were negative. There was no sign of reepithelialization because of the necrotic stromal bed. Six weeks later, lamellar keratectomy of the involved area was performed to remove the necrotic stroma. The specimen showed acute inflammatory cell infiltration, but no bacterium or other abnormality was found. Epithe-

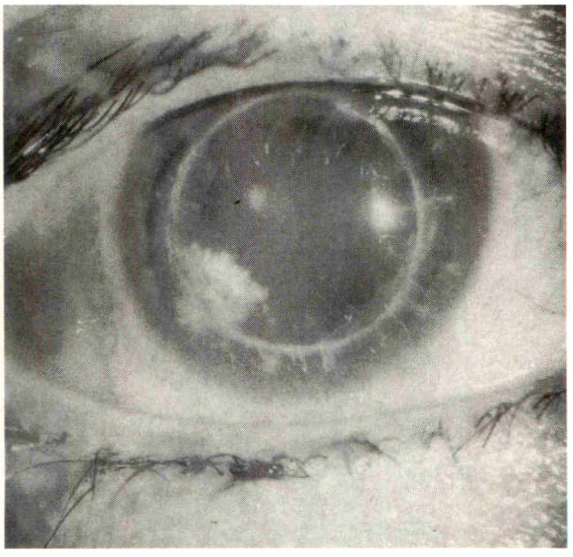

Fig. 1 (Hu). Crystalline anterior stromal infiltrate with exposed stitch at the 8 o'clock meridian and lack of surrounding inflammation.

lialization was complete two weeks after the operation and has remained stable.

Gorovoy and associates[2] reported that long-term corticosteroid therapy inhibited inflammatory response to the bacterial colonization in this infection. This is supported by our patient who developed suppurative inflammation upon cessation of corticosteroid therapy.

Pseudomonas species had been reported to be the causal agents of infectious crystalline keratopathy,[3] although not the species of *P. aeruginosa*. Because many microorganisms besides *S. viridans* are found to cause infectious crystalline keratopathy,[3-5] thorough microbiologic study and proper antibiotic treatment are mandatory in the management of this disease.

Fig. 2 (Hu). The same eye as seen in Figure 1, two weeks after cessation of corticosteroid therapy and initiation of fortified topical antibiotic treatment, showing suppurative process with marked conjunctival congestion.

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Penetrating Keratoplasty After Scleral Patch Graft

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Eye banking in the United States provides ophthalmologists with an efficient system for obtaining donor corneas for penetrating keratoplasty. In 1988, the Eye Bank Association of America provided donor tissue for over 36,000 corneal transplants.[1] Unfortunately, many foreign countries lack a structured system for supplying donor tissue. We treated a patient from Chiang Mai, Thailand in whom this problem was temporarily remedied through the use of a scleral patch graft.

A 40-year-old woman had blurred vision three days after an insect flew into her left eye. The patient noted a purulent discharge along with increasing pain and photophobia. Visual acuity was L.E.: 20/80. A 3-mm central corneal ulcer was noted on slit-lamp examination. No scrapings or cultures were obtained at this time, and she was treated with a ten-day regimen of topical tobramycin eyedrops. There was symptomatic improvement.

Three weeks later blurred vision, pain, and photophobia returned. Visual acuity was L.E.: 20/80, and a central corneal ulcer was again noted. Scrapings of the ulcer margins disclosed rare polymorphonuclear leukocytes but no organisms. The patient was hospitalized and given topical and systemic cephalosporin and aminoglycoside. All cultures were negative. Two days after admission a corneal perforation occurred and was immediately repaired with a cyanoacrylate tissue adhesive. The adhesive fell off after one week and the anterior chamber became flat. Her ophthalmologist in Chiang Mai (E.C.) performed a scleral patch graft with frozen homologous tissue. No donor corneas were available (Fig. 1). The patch obscured her central visual axis and was held securely in place by 10.0 nylon suture. Visual acuity was L.E.: hand motions.

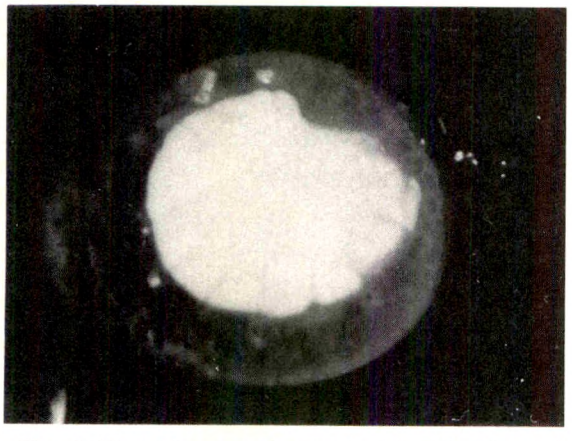

Fig. 1 (Van Meter and associates). Scleral patch graft obscuring central visual axis three weeks postoperatively.

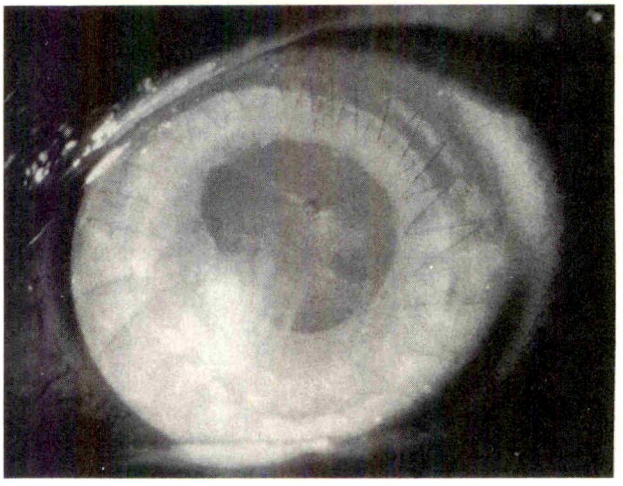

Fig. 2 (Van Meter and associates). Clear corneal graft two weeks after scleral patch graft removal.

Four months after the scleral patch was placed, a visiting surgeon with Project ORBIS (W.S.V.M.) performed a penetrating keratoplasty with a donor cornea from the eye bank at the University of Kentucky. The host corneal button included the perforating scleral patch graft and surrounding sutures. The operation was without complication, and the patient has undergone an unremarkable postoperative period on topical corticosteroids without allograft reaction (Fig. 2). Three months postoperatively visual acuity was L.E.: 20/30.

This case raises two important points. First, it underscores the need for organized eye banking in most third-world countries. Many ophthalmic surgeons outside the United States are well trained in techniques of keratoplasty but lack access to transplantable donor corneas. If an eye banking network were implemented, many potentially blinding corneal disorders could be alleviated. If no donor tissue is available, a scleral patch graft might be temporarily used until a keratoplasty could be performed. This procedure would enable emergency perforations to be stabilized until suitable donor corneal tissue became available.

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Intracorneal Ophthalmomyiasis

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This study was supported in part by grants from the Retina Research Foundation, the Lions Eye Bank, Houston, Texas (R.L.F.) and the Lions Eye Bank for Long Island, Manhasset, New York (H.D.P., E.D.D.).

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Two cases of corneal involvement in ophthalmomyiasis, a rare and potentially ominous condition in which fly larvae invade the eye, have been reported.[1,2] We treated a patient who had a significant inflammatory stromal reaction adjacent to a dead parasite.

A 46-year-old woman, referred for corneal consultation after her ophthalmologist noted an unusual corneal lesion, had blurring of vision and redness of her right eye for one month. Examination showed an uncorrected visual acuity of R.E.: 20/40 and L.E.: 20/50. The conjunctiva in the right eye showed moderate injection. Slit-lamp examination of the right cornea showed a white linear scar, 2 mm long, extending from the superficial cornea to the site of a curvilinear elongated foreign body measuring 1 mm long by 0.2 mm wide located at the junction of the anterior one third and posterior two thirds of the stroma. A prominent cellular infiltrate surrounded this foreign body that clinically appeared to resemble a fly larva, possibly *Cuterebra* species (Fig. 1). The anterior chamber showed trace flare and rare cells. The patient was treated with prednisolone acetate solution, one drop every two hours for one week with no change. An excisional biopsy was performed, and histopathology confirmed the diagnosis of intracorneal ophthalmomyiasis. Embedded in the scar was a periodic acid-Schiff stain-positive spine measuring 30 μm long by 8 μm wide (Fig. 2). Six months postoperatively, uncorrected visual acuity was R.E.: 20/30 − 1.

Newman and associates[1] described a patient who had a dead parasite, exhibiting little or no inflammatory reaction, as it lay adherent to the corneal endothelium for 27 months. The patient initially had a stinging sensation in the left eye progressing after 48 hours to a nongranulomatous iridocyclitis. After treatment, a parasite appeared adherent to the posterior corneal surface centrally. The left eye showed a trace anterior chamber flare and cells with no keratic precipitates. The cornea showed minimal stromal edema and no cellular infiltrates. No tracks or scars were noted beneath the retina. The patient was treated with a tapering

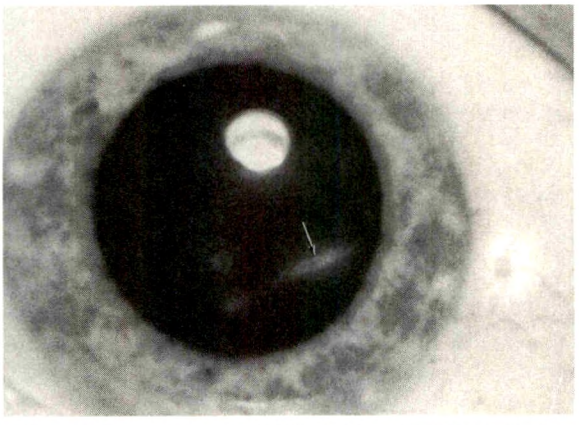

Fig. 1 (Perry, Donnenfeld, and Font). Clinical photograph showing intracorneal fly larva (arrow) (× 1).

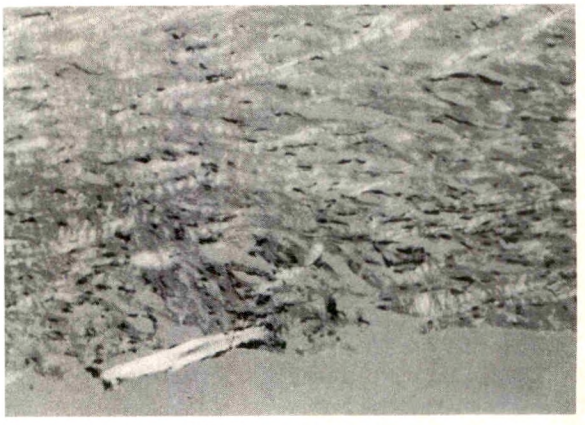

Fig. 2 (Perry, Donnenfeld, and Font). Polarized light showing remnant of parasite (× 50).

dosage of topical prednisolone acetate 1% for two weeks, with subsequent retreatment for four weeks. During the ensuing 27 months, visual acuity remained at 20/20 in the affected eye with no inflammation.

Laborde, Kaufman, and Beyer[2] described a patient who had no ocular complaints, but a larva was seen intracorneally in the deep stroma. Although several linear tracks were noted adjacent to the nonmotile larva, no inflammatory reaction surrounded the organism. The larva was removed through a paracentesis procedure and the patient retained visual acuity of 20/20 in the affected eye.

The occurrence of these three cases in the last three years may represent an increased awareness of this entity by experienced clinicians.

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Subretinal Endolaser Treatment of a Choroidal Bleeding Site

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Massive subretinal hemorrhage that elevates the fovea is associated with poor visual outcome.[1] The surgical treatment has been reported.[2-4] After surgical evacuation of subretinal hemorrhage caused by a choroidal neovascular membrane, recurrent subretinal hemorrhage may occur. An attempt to localize and treat a membrane in the immediate postoperative period may be complicated by hazy media and residual subretinal blood that may prevent adequate fluorescein angiography. We used the endolaser probe to treat a site of choroidal bleeding in the subretinal space immediately after evacuation of a subretinal clot.

A 57-year-old man with bilateral angioid streaks had a choroidal neovascular membrane extending partially into the left fovea. Visual acuity was R.E.: 20/20 and L.E.: 20/70. Krypton laser photocoagulation stabilized visual acuity in the left eye at 20/80. No systemic disorders associated with angioid streaks were found. Later, a recurrent membrane extending through the fovea resulted in visual acuity of L.E.: 20/200. Five months later, precipitous loss of vision in the right eye led to immediate re-examination. Visual acuity was R.E.: counting fingers at 2 feet. A large, subretinal hematoma that elevated the fovea and the inferotemporal vascular arcade was present (Fig. 1, left).

Understanding the poor visual prognosis without intervention, the patient elected to have surgical evacuation of the clot. The patient underwent a pars plana vitrectomy 6½ hours after visual loss. An inferotemporal retinotomy was made over the clot and the cannulated extrusion needle[5] was used in an unsuccessful attempt to aspirate the adherent clot. After the rettinotomy was enlarged, the forceps were used to grasp the clot and remove it in toto. Blood continued to ooze in the subretinal space. Elevation of the retina adjacent to the retinotomy showed a bleeding spot along an angioid streak. The retinotomy was retracted nasally to provide optimal visualization, and the endolaser probe was passed under the retina (Fig. 2). Ten argon blue-green laser burns were applied to the oozing site with immediate cessation of hemorrhage. A gas-fluid exchange was performed, and endolaser photocoagulation was applied around the retinotomy, sparing the fovea.

A five-month follow-up showed a trace amount of subretinal blood; however, no choroidal neovascularization was demonstrated by fluorescein angiography at ten, 15, and 19 weeks (Fig. 1, right). Visual acuity improved to R.E.: 20/50 by ten weeks and has remained stable for 26 weeks; the left eye has remained at 20/300. Visual field testing at 19 weeks showed a large superonasal scotoma in the right eye, corresponding to the retinotomy, with preservation of some central field vision. The left eye had a small dense central scotoma.

Presumably, the subretinal clot emanated from a choroidal neovascular membrane in an

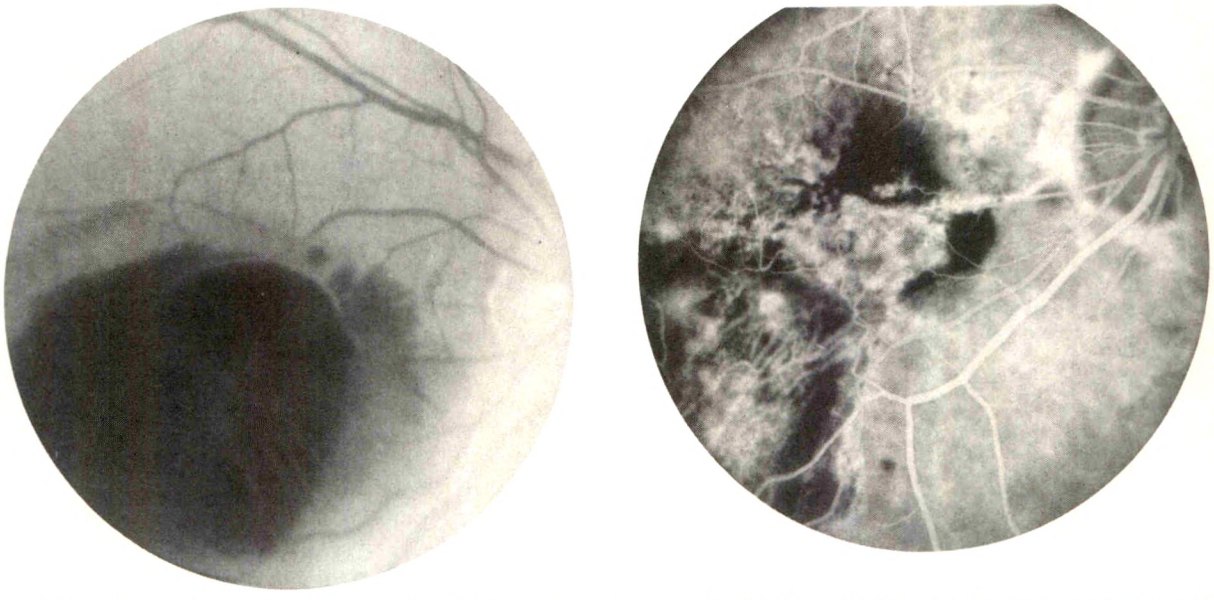

Fig. 1 (Thomas and Halperin). Left, Preoperative photograph showing thick subretinal hemorrhage and angioid streaks. Right, Postoperative fluorescein angiogram demonstrating a clearing of the subretinal space with normal fluorescence in the fovea and a large inferotemporal defect from the retinotomy and surrounding laser treatment. A trace amount of subretinal blood created blockage of fluorescence nasal to the fovea.

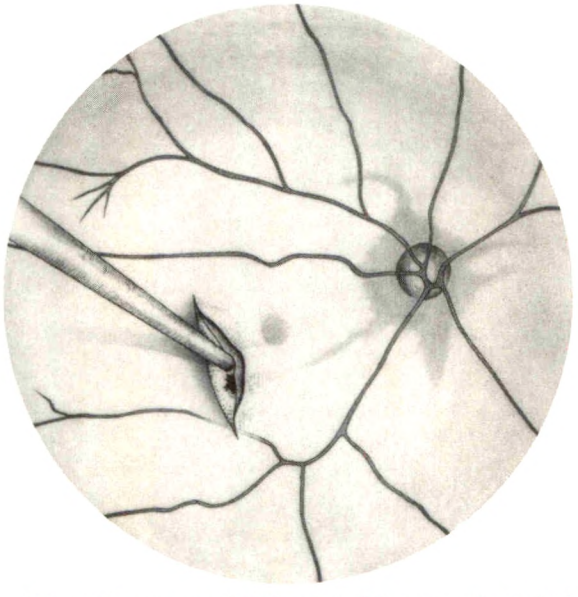

Fig. 2 (Thomas and Halperin). Diagram of surgical technique for subretinal endolaser treatment of a bleeding site showing a retinotomy with the endolaser probe under the retina. The probe was used to directly treat the retinal pigment epithelium without treating the retina.

angioid streak. However, no membrane was seen on repeated postoperative fluorescein angiography. We believe that the membrane was removed during the extraction of the adherent clot and the laser treated the site of ingrowth from the choriocapillaris. It seems less likely that treatment ablated a small membrane. The use of the endolaser beneath the retina in this manner may achieve hemostasis without damaging the neurosensory retina. The long-term visual prognosis remains unknown.

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Diabetic Retinopathy Associated With Acquired Immunodeficiency Syndrome

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Diabetic retinopathy in patients with insulin dependent diabetes mellitus develops proliferative changes and diffuse macular edema in association with many factors.[1] We treated a patient who had a dramatic worsening of background diabetic retinopathy in association with acquired immunodeficiency syndrome.

A 24-year-old man who was diabetic for 15 years and had moderate metabolic control was examined in November 1988. Visual acuity was R.E.: 20/30 and L.E.: 20/30. Ophthalmoscopy bilaterally showed background retinopathy, and fluorescein angiography disclosed focal macular edema (Fig. 1).

The patient returned in March 1989 because of bilateral visual loss. Visual acuity was R.E.: 20/100 and L.E.: 20/200. Ocular motility, pupillary reactions, and the anterior segments were normal. Ophthalmoscopic examination showed venous engorgement, multiple intraretinal hemorrhages, severe macular edema, and neovasculature of the optic disk. Fluorescein angiography showed markedly diffuse macular edema with retinal ischemia and leakage of the neovasculature (Fig. 2). Severe hypoglycemic episodes, changes in metabolic control, arterial hypertension, or renal failure had not occurred. The patient underwent panretinal photocoagulation in both eyes.

One month later the patient had diarrhea and dysphagia. *Candida* esophagitis was diagnosed. The patient admitted homosexual contacts and the human immunodeficiency virus test was positive. During admission, the patient developed bilateral *Pneumocystis carinii* pneumonia. His condition deteriorated, and he died from respiratory failure 50 days later.

Proliferative diabetic retinopathy can appear rapidly in the natural course of the disease,

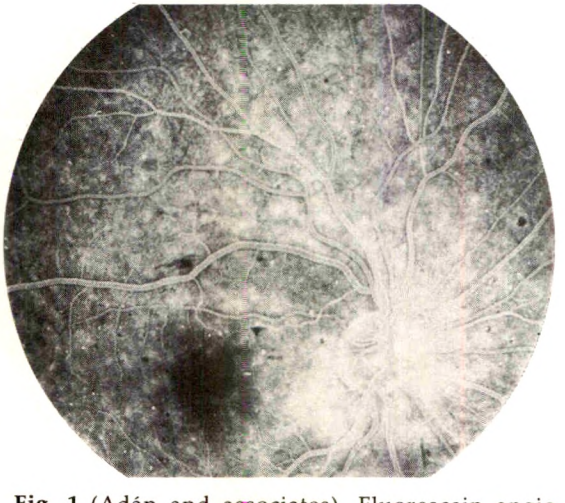

Fig. 1 (Adán and associates). Fluorescein angiogram, right eye, showing clusters of leaking microaneurysms.

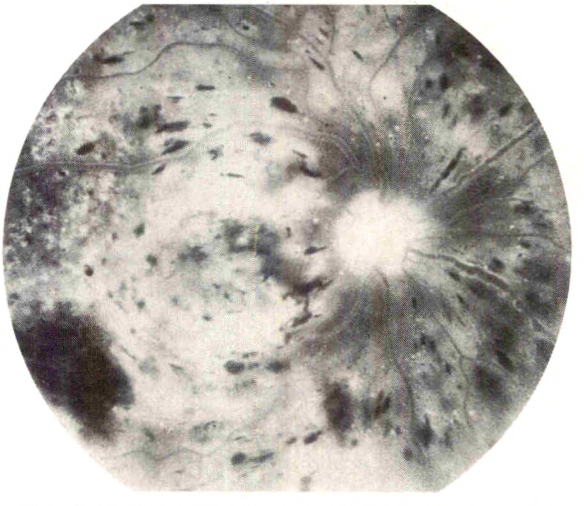

Fig. 2 (Adán and associates). Fluorescein angiogram, right eye, showing diffuse staining of the entire posterior retina and leakage of the neovasculature of the optic disk.

either spontaneously or associated with changes in metabolic control, severe hypoglycemia, or renal failure. Systemic factors such as fluid retention (cardiac or renal) and severe hypertension develop diffuse macular edema.[2] Vascular retinal changes in association with HIV infection have been reported.[3,4]

Retinal vascular occlusion in patients with AIDS could develop proliferative changes. Possible causes of vascular occlusion are circulating immune complex deposition and a direct toxic effect of a virus, including HIV, on the vascular endothelium. Further studies are needed, but the possibility that infection with HIV may aggravate diabetic retinopathy must be considered in the future.

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Linear Streak Lesions of the Fundus Equator Associated With Vogt-Koyanagi-Harada Syndrome

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Linear streak lesions over the equatorial area of the fundus are a peculiar finding appearing as an aggregation of histoplasmin spots[1] and have been considered characteristic of the presumed ocular histoplasmosis syndrome.[2,3] We noted such streak lesions in a patient with Vogt-Koyanagi-Harada syndrome.

A 27-year-old man had visual loss in both eyes and bilateral uveitis with exudative retinal detachment and pleocytosis in the cerebrospinal fluid. Vogt-Koyanagi-Harada syndrome was diagnosed by his primary physician. Despite treatment with local and systemic corticosteroids, the uveitis symptoms waxed and waned. The patient was referred to our institution three years later. Best-corrected visual acuity was 20/20 in each eye. Refraction was R.E.: −10.00 and L.E.: −8.00. The axial length of the globe was R.E.: 25.77 mm and L.E.: 26.86 mm (normal, 23.31 ± 0.73 mm). Both eyes showed mutton-fat keratic precipitates, moderate flare and cells in the anterior chamber, and a deformed pupil with partial posterior synechiae. The fundi were orange-yellow in appearance. Multiple linear streaks were present in the equator, and some atrophic focal chorioretinal lesions were visible over the paramacular or peripapillary area and periphery (Figure). No remarkable macular lesions were noted. Alopecia, poliosis, and vitiligo were found. Audiometry showed no hearing loss. Results of chest roentgenography showed no abnormalities. A histoplasmin skin test was negative. During two years of follow-up, inflammation in the anterior segment recurred occasionally, but the fundus remained unchanged.

Linear streak lesions are considered a fourth sign added to the common triad of presumed ocular histoplasmosis syndrome and were found in 5% of affected patients.[2] In our patient, a diagnosis of Vogt-Koyanagi-Harada syndrome was made according to the typical early manifestations of bilateral panuveitis, exudative retinal detachment, and pleocytosis in the cerebrospinal fluid; and the later appearance of an orange-yellow fundus, poliosis, alopecia, and vitiligo. The scattered atrophic focal chorioretinal lesions may be caused by damage in the retinal pigment epithelium and choriocapillaris in the sites of severe inflammatory foci in Vogt-Koyanagi-Harada syndrome.[4] A combination of presumed ocular histoplasmosis syndrome is unlikely because of the absence of a focal lesion in both maculae and the negative histoplasmin skin test. The disease is not endemic in Taiwan. Linear streak lesions have also been reported in

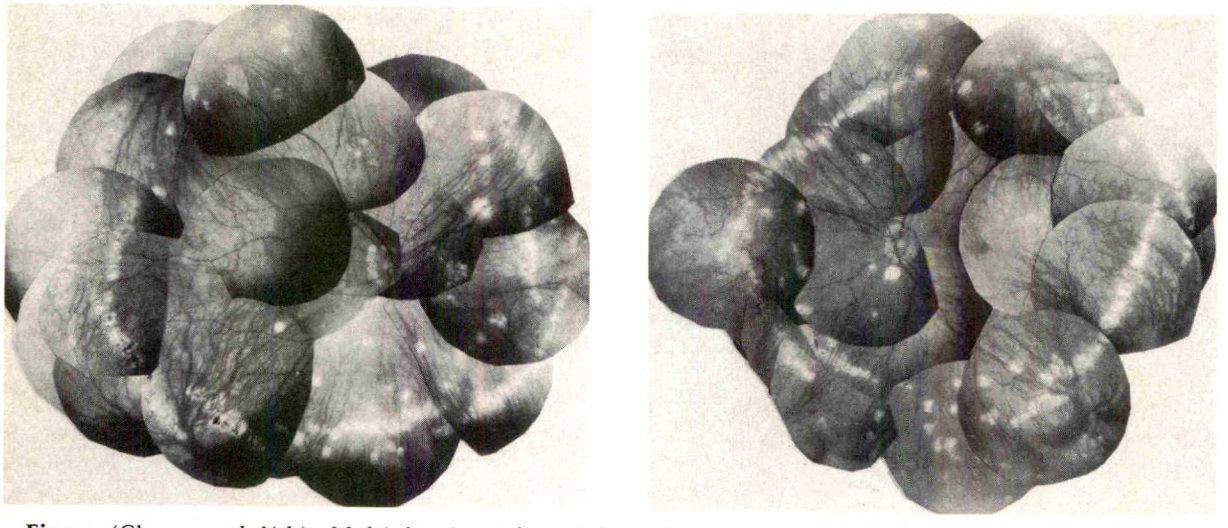

Figure (Chung and Yeh). Multiple circumferential or linear streaks in the equatorial region with an involvement of almost the entire circumference and an orientation parallel to the ora serrata in both the right eye (left) and the left eye (right) of a patient with Vogt-Koyanagi-Harada syndrome. Some atrophic focal chorioretinal lesions are scattered over the paramacular or peripapillary area and periphery.

patients with chorioretinopathy associated with anterior uveitis,[5] an entity recently termed "recurrent multifocal choroiditis." This indicates that the linear streak lesions may appear in a fundus with certain kinds of choroiditis and are not a finding seen uniquely in presumed ocular histoplasmosis syndrome. The pathogenesis of the streak lesions is unclear so far. The lesions' location in the equatorial region with an orientation parallel to the ora serrata suggests that the equatorial stretching because of an excessive axial elongation of the globe may be a predisposing factor.

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Diamond-Shaped Incision for Obtaining Dermis-fat Grafts

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Smith and Petrelli[1] reported the use of dermis-fat grafts for anophthalmic socket reconstruction in 1978, and subsequently refined the technique.[2,3] To obtain the dermis-fat graft, they recommend a circular skin incision with removal of a cylinder of dermis-fat tissue. Closure of the resultant circular defect can be difficult. Primary closure creates an unsightly puckered

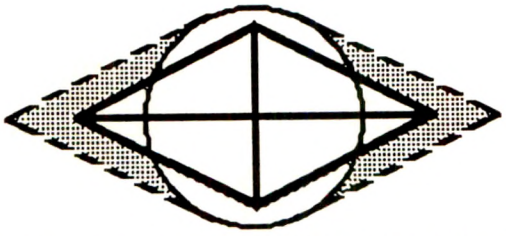


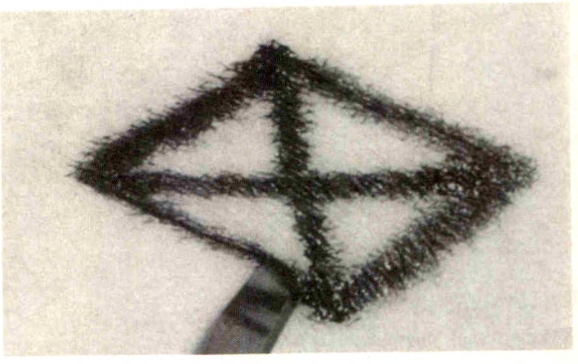
Fig. 1 (Meyer and Wobig). Geometric relationship between circular and diamond-shaped figures with equal surface area. Dotted lines represent additional tissue excision necessary to close circular defect.

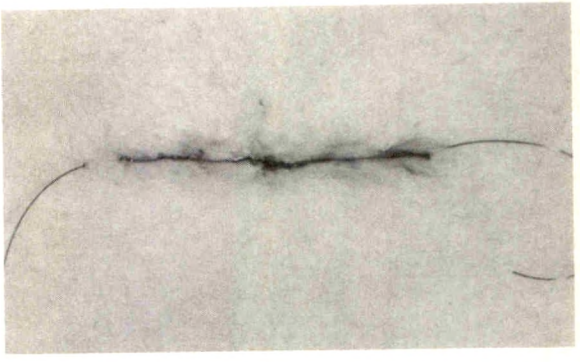
wound. Even an elliptical-shaped incision tends to pucker at its more eccentric margins. Numerous techniques to facilitate closure of circular defects have been reported.[4] These include excision of two triangles of tissue on either side of the circle, which are then discarded, as well as various types of skin advancement flaps.

We advocate a diamond-shaped incision to obtain the dermis-fat graft, with transplantation of the entire specimen. We use a diamond figure with an axial length twice its width. The area of this diamond figure is equal to the square of its axial width. To provide similar volume to that of the circular incision graft, use a diamond figure with an equivalent area, and maintain the same depth of the incision into fat. For example, a circular graft 1.6 cm in diameter has an area of 2.0 cm^2. A diamond figure with a width of 1.4 cm and length of 2.8 cm is equal in area (Fig. 1).

The graft is obtained after deepithelializing the surface (Fig. 2, top). The edges of the diamond-shaped donor site defect are directly approximated with interrupted, absorbable sutures through the deep dermis. The more superficial skin layers are then closed. The resultant wound is flat, linear, and unpuckered (Fig. 2, middle). The graft is transferred to the socket that has been prepared earlier. If the procedure is being done for a migrated or extruded orbital implant, a horizontal incision through the conjunctiva and anterior Tenon's capsule has been made. The diamond-shaped dermis-fat graft is positioned in the socket with its long axis horizontally. Conjunctiva and Tenon's capsule can then be approximated to the edge of the graft, or advanced over the surface of the dermis (Fig. 2, bottom).

We have used this technique on 81 patients, with a minimum follow-up of six months on all patients. Obtaining a diamond-shaped dermis-fat graft facilitates closure of the donor site, preserves tissue, and can provide the equivalent volume of traditional circular grafts for anophthalmic socket reconstruction.





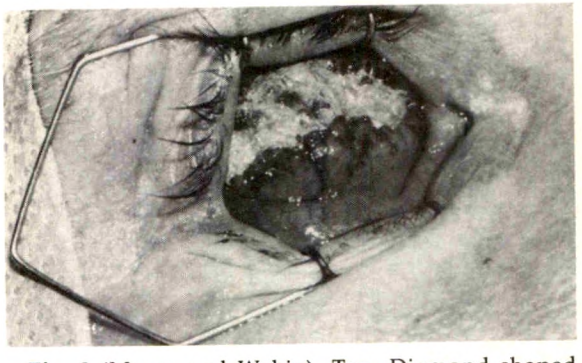


Fig. 2 (Meyer and Wobig). Top, Diamond-shaped incision to harvest dermis-fat graft. Middle, Direct closure of donor site. Bottom, Diamond-shaped dermis-fat graft sutured into anophthalmic socket.

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4. Patrinely, J. R., Marines, H. M., and Anderson, R. L.: Skin flaps in periorbital reconstruction. Surv. Ophthalmol. 31:249, 1987.

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Indirect Viewing of the Periphery of the Ocular Fundus Through a Plane Mirror—Correction

EDITOR:

I read with interest the letter "Indirect viewing of the periphery of the ocular fundus through a plane mirror," by E. Bartov, A. Alhalel, A. Spierer, and G. Treister (Am. J. Ophthalmol. 108:603, November 1989), and having tried it, I can recommend the technique. Figure 2, however, appears to be contradictory. The caption states that the temporal periphery is being examined. The illustration, however, shows the mirror held at the lateral canthus, with the examining lens clearly over the patient's nose. If the image of the fundus in the mirror is being examined, then indeed the nasal periphery is being visualized.

IZAK F. WESSELS, F.R.C.S.
Loma Linda, California

Reply

EDITOR:

We thank Dr. Wessels for his interest and recommendation of the technique described in our letter. His analysis of the mistake in Figure 2 is correct. We regret the obvious contradiction and agree with his criticism.

ELISHA BARTOV, M.D.
AMIR ALHALEL, M.D.
ABRAHAM SPIERER, M.D.
GIORA TREISTER, M.D.
Tel-Hashomer, Israel

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Oculoplastic, Orbital, and Reconstructive Surgery, vol. 2. Orbit and Lacrimal System. Edited by Albert Hornblass. Baltimore, Williams & Wilkins, 1990. 1,543 pages, index, illustrated. $139.95

Reviewed by BARTLEY R. FRUEH
Ann Arbor, Michigan

This second volume of the two-volume set covers orbital and lacrimal anatomy, physiology, diseases, examination and diagnostic techniques, and treatment. Dr. Hornblass draws on the experience of 90 individuals whose interests include ophthalmic plastic and orbital surgery, neuro-ophthalmology, ocular oncology, corneal and external disease, echography, pediatric ophthalmology, neurosurgery, plastic and reconstructive surgery, hematology and oncology, radiology, radiation therapy, and physics. The book is richly illustrated with high-quality drawings and photographs. The generally high quality of writing makes this an enjoyable book to read. Additionally, the considerable detail provided about most of the subjects makes this a worthwhile reference for all who have an interest in the orbit and tear drainage system, whether they be neophyte or expert.

Excellent organization facilitates the location of specific information. The text has 13 sections, nine covering orbital disease and four focusing on lacrimal disorders. There is occasional overlap of coverage, but this is deliberate. For example, consecutive chapters by Dr. Ellsworth and by Dr. Shields discuss rhabdomyosarcoma from different viewpoints. Three different perspectives on the evaluation of lacrimal outflow are provided.

Among noteworthy chapters that contain information not commonly found in other ophthalmology texts are the following: Motility Disorders in Orbital Disease; Craniofacial Surgery; Neurofibromatosis of the Orbit; Sarcoidosis; Amyloidosis of the Orbit and Adnexa; Radiation Therapy of the Neoplasms of the Eye and Orbit; Clinical Application of Photodynamic Therapy in Ophthalmology; and Transcranial Approach of the Orbit. The chapter on cardona keratoprosthesis, although well written and informative, does not seem appropriate either for the section on orbital surgery or for the volume.

As with any large text, there are weaknesses. In Chapter 100, one hopes that Table 100.7, which indicates that Graves' orbitopathy has a male preponderance of 4:1 and a poor prognosis for vision, suffers from typographic error and not erroneous belief. Chapter 108, Orbital Tumors of Osseous and Cartilaginous Origin, has either no information or minimal information about the management of each tumor; more emphasis on management would improve the chapter. Since this text is meant to be comprehensive, Chapter 117, Fractures of the Floor of the Orbit, should provide a more balanced view of the cause of floor fractures, not just mention the hydraulic theory. Some chapters contain suggested readings as well as references; however, Chapter 119, Naso-orbital Fractures, has only one reference and 60 suggested readings. Surely some of those readings could have been used as references to back up assertions made in the text.

In perspective, these faults are minor. I recommend this book to all physicians who have an interest in orbital and lacrimal disease and injuries because it provides both interesting reading and comprehensive information.

Extracapsular Cataract Microsurgery and Posterior Chamber Intraocular Lenses. Edited by Lucio Buratto. Milan, Fogliazza Editore, 1989. 756 pages, index, illustrated. $320

Reviewed by WAYNE E. FUNG
San Francisco, California

The editor of this text, Dr. Buratto, set out to define, illustrate, and resolve all of the potential problems that could be associated with modern cataract surgery. To do this, he described his own surgical techniques and their rationale in part 1 (257 pages). In part 2 (499 pages), the author asked 85 additional ophthalmic authors to cover limited aspects of extra-

capsular cataract surgery, intraocular lens implantation, and topics related to this major issue. The guest contributors are from 12 different countries: United States (23), Italy (13), France (eight), Great Britain (five), Switzerland (four), Germany (two), and one each from Belgium, the Netherlands, Israel, Japan, Spain, and Sweden. To translate and review the contributions, he had the help of three assistant editors. To illustrate the various problems and solutions, he enlisted the talents of a capable medical illustrator. Numerous color plates are distributed throughout the book.

Three fourths of the text is devoted to the surgical details of cataract surgery and intraocular lens implant by approximately 61 surgeons. "My Way" would be a good description of this major segment. The remaining text covers related topics. Subjects that are handled well are the following: surgical anatomy, intraocular lens types and intraocular inflammation, and lasers.

In a work that involves 86 authors from 12 different countries, editing and proofreading are extremely critical to ensure the quality of the final product. In this book, these two tasks have been treated lightly. Typographic errors are encountered on 90% of the pages. Publishing in a secondary language is difficult. Problems in expression are numerous, and inaccurate translations can be frustrating. Lastly, almost none of the illustrations are referenced in the text with which they are associated. The reader would do well just to look at the illustrations and not read the text.

These texts start with the basic premise that Tourette's syndrome is a common disorder that occurs in about 1% of the male elementary school population. This seems to be an exceptionally high percentage for a supposedly rare condition until one realizes that the authors are using a definition of Tourette's syndrome that has been broadened to include most of humankind's mysterious misbehaviors. Tourette's syndrome can, it seems, be found everywhere, often masquerading as an attention deficit, hyperactivity, dyslexia, conduct disorder, mood swings, panic attacks, sleep troubles, exhibitionism, compulsive eating, alcoholism, and the like. After reading these two books, you will begin to wonder if you have the syndrome yourself!

For the sake of their enthusiasm for the idea that many childhood behavior disorders are of genetic origin, and perhaps because it is psychologically useful to do so, the authors have grouped together an odd mixture of problems under the heading of "Tourette's syndrome." This grouping tends to blur the edges of the syndrome and will almost certainly confuse future research.

Nevertheless, this is well written, powerful material calculated to stun most parents with the shock of recognition and then finally to absolve them from any guilt they might feel, not only for having produced an abnormally troublesome child, but also for possibly having bungled the upbringing.

Tourette Syndrome and Human Behavior. By David E. Comings. Duarte, California, Hope Press, 1990. Softcover, 828 pages, index, illustrated. $39.95

Ryan. A Mother's Story of Her Hyperactive/Tourette Syndrome Child. By Susan Hughes. Duarte, California, Hope Press, 1990. Softcover, 153 pages, index. $9.95.

Reviewed by H. STANLEY THOMPSON
Iowa City, Iowa

The Book List

Atlas of Contemporary Surgery. Edited by Henry M. Clayman. St. Louis, C. V. Mosby Co., 1990. 1,060 pages, index, illustrated. $140

Binocular Vision and Ocular Motility. Theory and Management of Strabismus, ed. 4. By Gunter K. von Noorden. St. Louis, C. V. Mosby Co., 1990. 557 pages, index, illustrated. $92

The Eye in Systemic Disease. Edited by Daniel H. Gold and Thomas A. Weingeist. Philadelphia, J.

B. Lippincott, 1990. 710 pages, index, illustrated. $87.50

Fitting Guide for Rigid and Soft Contact Lenses. A Practical Approach, ed. 3. Edited by Harold A. Stein, Bernhard J. Slatt, and Raymond M. Stein. St. Louis, C. V. Mosby Co., 1990. 613 pages, index, illustrated. $55.95

Management of Orbital and Ocular Adnexal Tumors and Inflammations. Edited by Joseph A. Mauriello, Jr., and Joseph C. Flanagan. New York, Field & Wood Medical Publishers, Inc., 1990. 285 pages, index, illustrated. $145

Neuro-ophthalmology, ed. 2. Edited by Joel S. Glaser. Philadelphia, J. B. Lippincott, 1990. 557 pages, index, illustrated. $75

Sights and Sounds in Ophthalmology, vol. 7. Ocular Motility and Binocular Vision. By Kevin M. Miller, Hilda Capo, Robert A. Mallette, and David L. Guyton. St. Louis, C. V. Mosby Co., 1990. Slides, cassette tapes, softcover, 56 pages, index. $250

Stedman's Medical Dictionary, ed. 25. Edited by William R. Hensyl. Baltimore, Williams & Wilkins, 1990. 1,784 pages, illustrated. $38.95

The Theory of Intelligence. A Sensory-Rational View. By Thorne Shipley. Springfield, Illinois, Charles C Thomas, 1990. 101 pages, illustrated. $24.75

Transactions of Symposium on Oculoplastic Surgery Strabismus and Pediatric Ophthalmology. Edited by Barrett G. Haik. Thorofare, Slack, Inc., 1990. Softcover, 290 pages, illustrated. $65

Wills Eye Hospital. Office and Emergency Room Diagnosis and Treatment of Eye Disease. Edited by Mark A. Friedberg and Christopher J. Rapuano. Philadelphia, J. B. Lippincott, 1990. Softcover, 457 pages, index. $37.50

Meetings

The Sixth Congress of the International Strabismological Association

The Sixth Congress of the International Strabismological Association took place March 11 to 16, 1990, in Queensland, Australia, as a satellite function of the International Congress of Ophthalmology. More than 200 ophthalmologists from 16 countries attended. The scientific program consisted of the Bielschowsky Lecture, two symposia, 48 papers, and 21 posters. The meeting was organized by W. Gillies (Melbourne, Australia) and D. Stark (Brisbane, Australia). The congress facilities, in the proximity of magnificent beaches, were superb.

The Bielschowsky Lecture, given by Professor Peter Bishop (Canberra, Australia), concerned control of eye vergence and anomalous retinal correspondence. The audience listened with rapt attention as this world-renowned neurophysiologist elegantly bridged the gap between the classic concepts of motor and sensory retinal disparity responses and modern psychophysics and oculomotor research. It became clear from this eloquent lecture that advances in our knowledge of the causes and phenomenology of strabismus must depend on close cooperation between basic and clinical scientists.

The Arthur Linksz Award was presented in absentia to Professor Elfriede Aulhorn (West Germany) for her contributions to the development of instrumentation for the study of strabismus and her research on the sensory aspect of normal and abnormal binocular vision.

The first symposium moderated by P. Fells (United Kingdom) dealt with a most controversial subject, whether to treat refractive accommodative esotropia by conventional means (glasses or contact lenses) as is customary in the United States, or, as has been proposed for several years by certain European researchers, by operating on the muscle in order to get rid of the need for the glasses. The participants were sharply split into a conservative camp (A. Jampolsky and G. K. von Noorden [United States], and M. Spiritus [Belgium]) and the proponents of surgery (P. V. Berard [France], M. Gobin

[Belgium], and A. Morteno [New Zealand]). The discussion was quite heated, and its essence was summed up by the moderator who concluded that the case for surgery has yet to be proven.

The second symposium concerned the use of botulinum toxin (Oculinum) for the treatment of endocrine ophthalmopathy, abducens palsy, and essential infantile esotropia. This symposium left me with the impression that additional studies are necessary before the role of this therapy in these conditions can be definitively established.

The free papers dealt with such diverse subjects as methods of strabismus examination, clinical research, various forms of esotropia and exotropia, amblyopia, nystagmus and abnormal head posture, and surgical techniques.

The transactions of this congress will be published in the summer of 1990 under the editorship of E. Campos (Italy).

At the business meeting, the membership voted in favor of a resolution to support the use of laboratory animals in research on strabismus, amblyopia, and related diseases.

As is usually the case at international meetings of this sort the social aspects were especially pleasant, highlighted by the opportunity to greet old friends from distant countries and to make new ones. The extraordinary friendliness of the people from "down under" and the kindness of our Australian hosts will be long remembered by everyone who attended this congress.

The newly elected president of the association, S. Awaya (Japan), was introduced by the outgoing president, G. K. von Noorden. Vice-presidents are E. Campos (Italy) and C. Sousa-Dias (Brazil). E. M. Helveston (United States) was elected secretary-treasurer.

The Seventh Congress of the association will convene in 1994 in Canada in conjunction with the next International Congress of Ophthalmology.

GUNTER K. VON NOORDEN

Obituaries

David Oliver Harrington

1904-1990

David Oliver Harrington was born in Ocean Park, California, Sept. 7, 1904, and died at his Pacific Heights home in San Francisco on Feb. 18, 1990. Raised in San Francisco, he received his entire undergraduate and medical training at the University of California (A.B., 1927; M.D., 1931; internship, 1930-1931; residency, 1931-1932). Dr. Harrington was the first ophthalmology resident physician at the University of California Hospital. Encouraged by Frederick Cordes, then chairman of the Department of Ophthalmology at the University of California School of Medicine, he traveled to Europe for additional training. There, Dr. Harrington initially served as Hospitant at the University of Vienna General Hospital and subsequently as a Fellow at the University of Edinburgh Royal Infirmary and at Moorfield's Hospital in London. In Edinburgh he worked with H. M. Traquair, learning the techniques of quantitative visual field examination and interpretation. This area of investigation was to become a lifelong interest for Dr. Harrington.

Upon his return to San Francisco he established a private practice in ophthalmology and became an instructor in the Department of Ophthalmology at the University of California Medical School. Here he also served in the Department of Neurosurgery under the directorship of Howard C. Naffziger. He had the opportunity to observe patients before as well as after neurologic surgery, thus correlating his visual field studies with the pathologic lesions that produced them. His service with the University of California continued for 40 years. He became emeritus professor in 1974 and then accepted an appointment to work with residents for another ten years, receiving two outstanding teacher awards. During his long career Dr. Harrington developed pioneering visual field screening devices and wrote more than 50 articles in the areas of neuro-ophthalmology and glaucoma. He was also the author of The Visual Fields, a textbook originally published in 1958 that was translated into 12 languages.

During World War II he served in the Navy as Chief of Ophthalmology for the Pacific Theater and was separated as a Commander. Dr. Harrington was a member of the American Board of Ophthalmology (1964-1973) and its chairman in 1973. He was vice-president of the American Academy of Ophthalmology and Otolaryngology in 1970. He served as a member of the editorial board of the Western Journal of Medicine and also as a governor of the American College of Surgeons. In 1977 he was elected president of the American Ophthalmological

Society and in 1981 he was the recipient of the Society's Howe medal.

Dr. Harrington was truly a gentle man with broad extramedical interests in music, photography, poetry, and in support of cultural events in San Francisco. His sensitivity and concern for humanity is exemplified by the following poem, written while he served in the Pacific Theater during World War II.

Sonnet To the Blind of Iwo Jima

What does it profit us whose sightless eyes
Will ne'er again behold but only sense
The glory of the Autumn leaves; the sighs
Of you who'll love when Spring the Senses tense?
Is there reward for us, now banned from light,
Whose earthly vision ended in the glare
Of bursting shells; the pall of smoke; the sight
Of blasted death and ashes in the air?
Give us the knowledge, though we cannot see,
That what we did on that bleak, worthless strand
Will not an end but a beginning be
Of vision in a better, freer land.
We've paid the price. Now can we surely ask
As recompense, completion of the task.

Dr. Harrington is survived by a son, Dr. Kevin Dodds Harrington of San Francisco, a daughter, Erin Harrington Van Speybroeck of Belmont, Massachusetts, and by eight grandchildren.

WM. H. SPENCER

Harold G. Scheie

1909-1990

Harold G. Scheie died March 5 in Philadelphia after a long illness. He was born in Brookings, South Dakota, March 24, 1909. He received the B.S. degree and the M.D. degree from the University of Minnesota. Dr. Scheie interned at the University of Pennsylvania Hospitals where he was a resident in the Department of Ophthalmology, and received the Doctor of Science degree from the University of Pennsylvania.

During World War II, Dr. Scheie was chief of ophthalmology of the 20th General Hospital in the China-Burma Theater and later at Crile General Hospital. He was subsequently named a brigadier general in the Army reserves and served as commanding general of the 303rd Hospital Center.

Dr. Scheie was a professor at the University of Pennsylvania and at the Graduate School of the University of Pennsylvania. He succeeded Francis Adler as the William F. Norris and George E. de Schweinitz Professor and chairman of the Department of Ophthalmology at the University of Pennsylvania in 1960. He was also chairman of the ophthalmology services at Philadelphia General Hospital, Childrens' Hospital, and the Veterans Administration Hospital. In 1972 he founded the Scheie Eye Institute.

Dr. Scheie was secretary and then chairman of the Section on Ophthalmology of the American Medical Association, and received the Prize Medal of the Section. The Section developed the Knapp awards for the best paper and the best exhibit under his direction and also had a large and active program committee. He served as president of the Pennsylvania Academy of Ophthalmology and Otolaryngology and vice president of the College of Physicians of Philadelphia, the National Society for the Prevention of Blindness, and the American College of Surgeons, which he also served as regent.

He was an honorary member of the Order of the British Empire. He received honorary doctorate degrees from Villanova University and the University of Pennsylvania, which also established the Scheie Research Professorship. A Scheie professorship was established at the University of Minnesota. Modern Medicine awarded him the Distinguished Achievement Award; the American Schools and Colleges Association, the Horatio Alger Award; the American Academy of Achievement, the Golden Plate Award. He received the Howe Awards of the American Ophthalmological Society and the University of Buffalo, the honor award of the American Academy of Ophthalmology and Otolaryngology, and the Strittmatter Award of the Philadelphia County Medical Society. Dr. Scheie gave many named lectures and was an honorary member of many foreign ophthalmological societies.

Dr. Scheie published widely and his name is

associated with two phenotypes of mucopolysaccharidosis I, the Hurler-Scheie syndrome, and a mild form, the Scheie syndrome. He popularized scleral cautery in glaucoma filtration procedures. Together with Francis Adler, he localized the site of the lesion in Adie's syndrome. He was co-author with Meyer Weiner of "Surgery of the Eye" and co-author with Daniel Albert of "History of Ophthalmology at the University of Pennsylvania" and two editions of a "Textbook of Ophthalmology." Two editions of his "Lecture Notes in Ophthalmology" were published. He served on the editorial board of the Archives of Ophthalmology and several other ophthalmic journals.

Dr. Scheie is survived by his wife, Mary Ann, and three children.

FRANK W. NEWELL

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

Transactions of the American Ophthalmological Society

All of the following are summaries of theses published in the "Transactions of the American Ophthalmological Society."

The use of liposome-encapsulated 5-fluoroorotate for glaucoma surgery: 1. Animal studies. Alvarado, J. A. (Dept. Ophthalmol., U-490, Univ. California, San Francisco, San Francisco, CA 94143). Trans. Am. Ophthalmol. Soc. 87:489, 1989.

The author studied the histologic characteristics of normal wound healing in rhesus monkeys. Healing of the sclera is similar to healing of other soft tissues with scar formation in two weeks. An antimetabolite, 5-fluoroorotate, a derivative of 5-fluorouracil was instilled in a group of monkeys. This drug is three times more potent than 5-fluorouracil. In one experiment the drug was encapsulated in a liposome system at the time of surgery. An injection was given in another group one week before filtering surgery. The encapsulated liposomal 5-fluoroorotate was highly effective in preventing the formation of scars and promoting the development of functional blebs. Drug administration before filtering surgery seemed to be more effective than injection at the time of filtering surgery. (7 figures, 6 tables, 55 references)—David Shoch

Müller cell alterations from long-term ambient fluorescent light exposure in monkeys: light and electron microscopic, fluorescein and lipofuscin study. Berler, D. K. (5454 Wisconsin Ave., Chevy Chase, Maryland 20815). Trans. Am. Ophthalmol. Soc. 87:515, 1989.

Both eyes of eight cynomolgus monkeys were exposed to fluorescent light for 12 hours daily for four weeks. One eye was enucleated four days after exposure, one eye was enucleated two weeks after exposure, and the remaining 14 eyes were enucleated at the end of exposure. One eye of each of two monkeys was exposed to the light of an indirect ophthalmoscope for 15 minutes. The exposed eyes and the control eyes were enucleated 48 hours after exposure. The Müller cells were vacuolated in all experimental eyes and not affected in the control eyes. No other retinal cells showed any change and the retinal pigment epithelium was normal. The light-induced Müller cell change was roughly the area of distribution of macular xanthophil. There were associated intracellular and extracellular fluid accumulations but the lipofuscin content was not changed in the experimental eyes. Fluorescein angiography did not show any leakage or staining and the fluid accumulation cannot be considered cystoid macular edema. Possibly Müller cell vacuolization is an early indicator of retinal phototoxicity. (34 figures, 5 tables, 172 references)—David Shoch

Conjunctival provocative tests: a model of human ocular allergy. Friedlaender, M. H. (Scripps Clin. Med. Group, 10666 N. Torrey Pines Rd., La Jolla, CA 92037). Trans. Am. Ophthalmol. Soc. 87:577, 1989.

The allergic response of the conjunctiva was tested in 26 allergic subjects and ten nonallergic subjects. The allergic subjects all had a history of allergy to cats or ragweed and the control subjects did not. The allergic response was graded by the severity of hyperemia, chemosis, and itching. Each sign was graded on a basis of 0 to 4 to provide a maximum score of 12. The dose of allergen required to elicit a response was much greater for the conjunctiva than for skin. Thus, in a cat-sensitive individual, the amount of allergen needed to produce a 7-mm or greater skin reaction was from 0.05 to 50 allergy units/ml. The amount of cat dander allergen needed to elicit a moderate conjunctival reaction ranged from 50 to 50,000 allergy units/ml. The predominant inflammatory cell present between 15 minutes and 24 hours was the neutrophil, which accounted for between 70% and 90% of inflammatory cells. Eosinophils accounted for most of the remainder and ranged from 7% to 24%. There did not appear to be a biphasic response to the allergen. The conjunctival responses can be standardized to provide information about immunologic events that occur in allergic inflammation. (6 figures, 10 tables, 51 references)—David Shoch

Timolol treatment prevents or delays glaucomatous visual field loss in individuals with ocular hypertension: a five-year randomized, double-masked, clinical trial. Kass, M. A. (660 S. Euclid Ave., St. Louis, MO 63110). Trans. Am. Ophthalmol. Soc. 87:598, 1989.

Individuals with ocular hypertension develop glaucomatous visual field loss at an approximate rate of between 0.5% and 1% per year. To test whether reducing the level of ocular hypertension would reduce this incidence of glaucoma 62 subjects with ocular hypertension received timolol 0.25% twice daily in one eye and diluent twice daily in the fellow eye. If the intraocular pressure during the study was more than 20 mm Hg, the treatment of that eye was increased to either 0.5% timolol twice daily or diluent twice daily depending on the original randomized scheme. Of the 62 patients, 19 did not complete the five-year follow-up and did not develop visual field loss. Forty-three patients either completed the minimum five-year follow-up or developed visual field loss. When the code was broken it was found that timolol reduced the intraocular pressure of the treated eye by 4.9 ± 3.4 mm Hg. Additionally, it reduced the pressure in the contralateral eye by 2.9 ± 3.1 mm Hg. The difference between the treated and the untreated eyes was 2.3 ± 2.6 mm Hg. Visual field loss developed in four timolol-treated eyes and in ten placebo-treated eyes ($P = .039$). Progression of optic disk cupping was noted in four treated and eight untreated eyes ($P = .11$). The mean increase in optic disk pallor was 0.86% ± 2.4% in timolol-treated eyes and 1.8% ± 3.6% in the placebo-treated eyes. This difference was statistically significant ($P = .04$). This study provides evidence that medical treatment prevents or delays the onset of glaucomatous visual field loss and optic disk damage in individuals with ocular hypertension. The magnitude of the protective effect was partially obscured by the contralateral reduction in intraocular pressure in the placebo-treated fellow eyes. (1 figure, 9 tables, 51 references)—David Shoch

The surface of the corneal graft: in vivo color specular microscopic study in the human. Lemp, M. A. (Dept. Ophthalmol., Georgetown Med. Ctr., 3800 Reservoir Rd., N.W., Washington, D.C. 20007). Trans. Am. Ophthalmol. Soc. 87:619, 1989.

Using color specular microscopy of the corneal epithelium, high-speed color film, and topical fluorescein and rose bengal, the author distinguished morphologic features of surface cells and properties of cell membranes on the surface of corneal grafts. The most common finding was central vortex keratopathy. There was also redirection of cells in a palisading pattern around sutures, a piling up of cells at the wound junction, and filaments and mucous plaques near the suture line. The vortex keratopathy and the palisading of cells around sutures disappeared after suture removal. The central epithelial cell structure two years or more after surgery resembled that of normal cornea. The author proposed a differential sliding of epithelium from the periphery to the center with the epithelium drawn centripetally by preferential loss of surface cells in the corneal center. The central vortex keratopathy may be an exaggeration of normal cellular movement that occurs when differential sliding of cells is pronounced in corneal grafts. (4 figures, 6 tables, 117 references)—David Shoch

Mapping the gene for X-linked cataracts and microcornea with facial, dental, and skeletal features to Xp22: an appraisal of the Nance-Horan syndrome. Lewis, R. A. (Dept. Ophthalmol., Baylor College of Med., 6501 Fannin, NC 206, Houston, TX 77030). Trans. Am. Ophthalmol. Soc. 87:658, 1989.

The human genome is estimated to contain about three billion base pairs (3×10^9 bp) of deoxyribonucleic acid (DNA). Each normal individual inherits two copies of this genome, in which the DNA is packed as 23 pairs of chromosomes, containing between 30,000 and 150,000 different gene sequences. If the average gene includes 40 kilobases (kb) and the average chromosome 100,000 kb, then even under the highest resolution of microscopic visualization of the human karyotype at the 1,000 band level of modern cytogenetics, the average chromosomal band would contain about 2,500 kb or approximately 60 genes. A change of a single nucleotide in one of the two genomic copies can mean the difference between normal life and disease or possibly early death.

The author evaluated the association of congenital cataracts and microcornea with the X chromosome. The affected males with congenital cataract and microcornea have dense congenital cataracts involving the posterior Y-suture of the lens and corneas that average 9 mm in the horizontal diameter. Additionally affected males have dental malformations and some facial alterations. Female heterozygotes can be distinguished by the presence of milder forms of these same phenotypic features. The horizontal corneal diameter in female carriers averages 10.5 mm, about half way between the normal corneal diameter and that of affected males. By means of restriction endonucleases the author generated DNA fragments of different lengths. He showed that the locus for X-linked cataracts and microcornea is located at band 22.2 of the short arm of the X chromosome. Now that the position of this gene is known it may be possible to isolate the gene and define its molecular structure. Ideally one would define a missing gene product and be able to treat the disease by replacement of the missing gene. (13 references, 8 tables, 113 references)—David Shoch

The role of apraclonidine hydrochloride in laser therapy for glaucoma. Robin, A. L. (4419 Falls Road at Cold Spring Lane, Baltimore, MD 21211). Trans. Am. Ophthalmol. Soc. 87:729, 1989.

Increases in intraocular pressure commonly follow laser iridotomy and trabeculoplasty. Although the mechanism of this increase in pressure is unknown it may be caused by the release of particulate matter that blocks the outflow channels. Topical apraclonidine appears to diminish the postoperative intraocular pressure increase consistently after laser surgery. To study this drug more carefully the author compared the effects of apraclonidine with glaucoma medications commonly used after argon laser trabeculoplasty. Additionally, he compared the same drugs after argon laser iridotomy, and finally, he investigated the effects of 1% apraclonidine on iris bleeding after YAG laser iridotomy in the monkey. The first two studies showed that 107 of 125 (86%) eyes treated with apraclonidine had no intraocular pressure increase during the first three postoperative hours; 12 of 35 (60%) of the eyes treated with timolol had no intraocular pressure increase; 16 of 37 (43%) eyes treated with pilocarpine had no intraocular pressure increase; eight of 31 (26%) eyes treated with acetazolamide had no pressure increase, and 15 of 32 (47%) eyes treated with dipivefrin had no pressure increase. Apraclonidine reduction of bleeding in primate eyes after laser iridotomy was not statistically significant. (6 figures, 10 tables, 98 references)—David Shoch

An analysis of corneal endothelial and graft survival in pseudophakic bullous keratopathy. Sugar, A. (Kellogg Eye Ctr., 100 Wall St., Ann Arbor, MI 48105). Trans. Am. Ophthalmol. Soc. 87:762, 1989.

About 5% of eyes in which either an iris-supported lens or an anterior chamber lens was inserted developed bullous keratopathy. Fewer eyes develop bullous keratopathy after insertion of posterior chamber lenses. There is, however, a significant incidence of bullous keratopathy after intraocular lens implantation, estimated at about 0.5%. To study the best treatment for this complication, 469 patients undergoing penetrating keratoplasty for pseudophakic bullous keratopathy were divided into groups as to whether the intraocular lens was retained, removed, or exchanged. Specular microscopy was performed on 390 patients. The failure rate varied in the three groups between 16% and 24% but these differences were not statistically significant. Within the group in which the lenses were retained the incidence of failure was 6% with retained posterior chamber lenses and approximately 30% with retained anterior chamber and iris-supported lenses. With lens exchange the failure rate was 8% for sutured posterior chamber lenses, 5% for one-piece anterior chamber lenses, and 24% for closed-loop anterior chamber lenses. Final visual acuity was best for retained posterior chamber intraocular lenses and for exchanged one-piece anterior chamber intraocular lenses. Specular microscopy findings at one year were predictive of longer term survival results. The least cell loss was for retained and exchanged posterior chamber lenses and exchanged one-piece anterior chamber lenses. (7 figures, 4 tables, 175 references)—David Shoch

Ultraviolet radiation and the eye: an epidemiologic study. Taylor, H. R. (Johns Hopkins Hosp., Baltimore, MD 21205). Trans. Am. Ophthalmol. Soc. 87:802, 1989.

To study the effect of the near ultraviolet on the eye the author studied Chesapeake Bay water men who spent most of their lives out of doors. Their ultraviolet exposure was quantified for each year of life over the age of 16 on the basis of an occupational history combined with laboratory and field measurements of ocular ultraviolet B (320 to 290 nm) exposure. Individuals with cortical lens opacities had a 21% higher ultraviolet B exposure at each year of life than those without such opacities. A doubling of ultraviolet B exposure led to a 60% increase in the risk of cortical cataracts. Those with a high annual ultraviolet B exposure increased their risk of cortical cataracts more than threefold. No association was found between nuclear lens opacities or macular degeneration and ultraviolet B exposure. To reduce the exposure to the eyes from ultraviolet rays the author recommended wearing hats with brims and the use of plastic lenses, either tinted or untinted with wraparound side shields. (14 figures, 12 tables, 129 references)—David Shoch

Development of a system for excimer laser corneal surgery. Waring, G. O. (Dept. Ophthalmol., Emory Univ., 1327 Clifton Rd., N.E., Atlanta, GA 30322). Trans. Am. Ophthalmol. Soc. 87:854, 1989.

The development of pulsed lasers, particularly argon fluoride which is active at 193 nm permits precise excision of corneal tissue. Additionally these excimer lasers can be coupled to a computer to provide exact repetitive surgical procedures. Excimer lasers have many drawbacks. It is technically difficult to control the toxic fluoride gas, to create a homogeneous beam, and to deliver the beam in an effective configuration. Effective linear corneal excisions must be 100 to 150 nm wide. The excisions fill with an epithelial plug that persist months to years. There is some subepithelial scarring and some regression of the corneal flattening during the postoperative course. Wound healing may decrease the refractive effect of the initial application and stromal scarring may cause light scattering and image degradation. The mechanical variability and delivery of laser pulses is gradually being standardized and excimer laser refractive keratoplasty may still prove effective, safe, predictable, and stable. (45 figures, 7 tables, 94 references)—David Shoch

Downbeat nystagmus characteristics and localization of lesions. Yee, R. D. (Dept. Ophthalmol., Indiana Univ., 702 Rotary Circle, Indianapolis, IN 46223). Trans. Am. Ophthalmol. Soc. 87:984, 1989.

The most frequent causes of downbeat nystagmus were infarction, cerebellar and spinocerebellar degenerations, multiple sclerosis, and developmental anomalies of the pons and cerebellum. Toxicity from anticonvulsant drugs was an occasional cause. The localization of the lesions included the cerebellum in 88% of the patients. Recordings of horizontal ocular movements demonstrated a pattern of abnormality characteristic of damage to the midline structures of the cerebellum. There was impaired pursuit movements, impaired oculokinetic nystagmus, and inability to suppress vestibulocular reflexes in 90 of 91 (99%) patients with downbeat nystagmus. Downbeat nystagmus is usually produced by lesions in the cerebellum that also damage pathways which control horizontal tracking and visual-vestibul-ocular interactions. (11 figures, 12 tables, 82 references)—David Shoch

David Shoch
1918-1990

David Shoch, president of the Ophthalmic Publishing Company, editor of the Abstract section of THE JOURNAL since 1964, and professor of ophthalmology and previous department chairman at Northwestern University Medical School, died May 8, 1990. An obituary will appear next month.

NEWS ITEMS

Send News Items to
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The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

American Academy of Ophthalmology: Future Meetings

Future meetings of the American Academy of Ophthalmology are as follows:

Oct. 28–Nov. 1, 1990—Atlanta
Oct. 13–17, 1991—Anaheim
Nov. 8–12, 1992—Dallas
Nov. 14–18, 1993—Chicago
Oct. 30–Nov. 3, 1994—San Francisco
Oct. 29–Nov. 2, 1995—Atlanta
Oct. 6–10, 1996—Chicago (Centennial)
Oct. 26–30, 1997—San Francisco
Nov. 8–12, 1998—New Orleans

International Society of Ocular Trauma: Second International Congress

International Society of Ocular Trauma: Second International Congress will be held April 2–5, 1992, in Geneva, Switzerland. For further information, write KENES, Conference Organizers, P.O. Box 50006, Tel Aviv 61500, Israel; telephone 972 3 654571; fax 972 3 655674.

University of Vienna: International Alpine Vitreoretinal Symposium

University of Vienna: International Alpine Vitreoretinal Symposium will be held Jan. 6–13, 1991, in Telfs/Tyrol, Austria. For further information, write Prof. Dr. S. Binder, c/o Vienna Medical Academy, Alser Strasse 4, A-1090 Vienna; telephone 0222/42 13 83; fax 0222/42 13 83 23.

Alcon Research Institute: 1990 Vision Research Awards

The Alcon Research Institute announced vision research awards of $50,000 to each of the following: Ata. A. Abdel-Latif, Medical College of Georgia; Bernard Becker, Washington University School of Medicine; Ennio Lucio Benedetti, Institut Jacques Monod, Paris, France; Anthony J. Bron, Oxford, England; Richard A. Farrell, Johns Hopkins University; Igal Gery, National Institutes of Health; Peter Gouras, Columbia University; Torsten Krakau, Malmö Allmanna Sjukhus, Malmö, Sweden; Jerome R. Kuszak, Rush-Presbyterian St. Luke's Medical Center; Dominic Man-Kit Lam, Baylor College of Medicine; Matthew LaVail, University of California, San Francisco; A. A. Moscona, University of Chicago; and Johannes W. Rohen, Anatomisches Institut, Erlangen, West Germany.

The Alcon Research Institute is dedicated to vision research. The Institute is funded by Alcon Laboratories, Inc., and it is directed by an independent advisory committee: Steven M. Podos, chairman; Anders Bill, Uppsala Universität; Hans Bloemendal, Universiteit Van Nijmegen; Henry F. Edelhauser, Emory University School of Medicine; Morton F. Goldberg, Wilmer Institute; Yoshiaki Kitazawa, Gifu University of Medicine; Howard M. Leibowitz, Boston University Medical Center; Elke Lutjen-Drecoll, University Erlangen—Nürnberg; Neville N. Osborne, University of Oxford; and Abraham Spector, Columbia University.

Each year the committee selects individuals who have made important contributions to vision research. A monetary award is given with the expectation that the awardees will apply it to further their research.

Doheny Eye Institute: Diabetes and the Eye –22nd Annual Doheny Meeting

Doheny Eye Institute: Diabetes and the Eye–22nd Annual Doheny Meeting will be held Sept. 27 and 28, 1990, in Los Angeles, California. For further information, write Dave Carpenter, Director CME, Doheny Eye Institute, 1355 San Pablo St., Los Angeles, CA 90033; telephone (213) 224-5580.

Presbyterian Healthcare System: Cataract 1990

Presbyterian Healthcare System: Cataract 1990 will be held Sept. 7, 1990, in the Campbell Center at the Doubletree Hotel in Dallas, Texas. For further information, write Office of Continuing Medical Education, Presbyterian Healthcare System, 8200 Walnut Hill Ln., Dallas, TX 75231; telephone (214) 696-8458.

Personals

Joseph Caprioli

The 1989 Jules Francois Prize, sponsored by Merck Sharp and Dohme-Chibret, of 300,000 Belgian francs was awarded to Professor Joseph Caprioli, from the Yale University School of Medicine. A part of Professor Caprioli's work concerns the mechanisms of optic nerve damage in glaucoma. According to Dr. Caprioli, the Jules François Prize will provide him "with additional resources and freedom to pursue this avenue of research further."

Michael Van Buskirk

Michael Van Buskirk has been appointed chairman of the Department of Ophthalmology at Good Samaritan Hospital and Medical Center, in Portland, Oregon.

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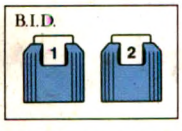
In a world of hype and exaggeration, new Betagan® 0.25% is that rare exception. It is not bigger or faster and it won't give you more.

What new Betagan 0.25% gives you, in fact, is less. But, that's what makes it an excellent addition to your practice.



Because Betagan 0.25% is safe and effective and gives you, for the first time, the option of beginning your patients on 0.25% or 0.5% Betagan.

So consider starting your newly diagnosed open-angle glaucoma or ocular hypertension patients with Betagan 0.25%. It's the one with the levobunolol concentration on the bottom and the commitment to your patients on top.

Betagan® 0.25%
(levobunolol HCl)
Liquifilm® sterile ophthalmic solution with C Cap™ Compliance Cap B.I.D.

As with other topically applied ophthalmic drugs, Betagan may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration.

Betagan®
(levobunolol HCl) 0.25%
Liquifilm® sterile ophthalmic solution with
C Cap™
COMPLIANCE CAP
B.I.D.

See page 44 for brief prescribing information